UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

PARATEK PHARMACEUTICALS, INC.,
75 Kneeland Street, Boston, MA 02111

Plaintiff,

v.

HONORABLE DAVID KAPPOS
Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office
PO Box 15667, Arlington, VA 22215
Madison Building East, Rm. 10B20
600 Dulany Street, Alexandria, VA 22314

Defendant.

Civil Action No. _____

COMPLAINT

The plaintiff, Paratek Pharmaceuticals, Inc., complains against the Honorable David Kappos, as follows:

NATURE OF THE ACTION

1. In this patent term adjustment case arising under 35 U.S.C. § 154(b)(4), Paratek seeks a judgment ordering the director of the United States Patent and Trademark Office ("USPTO") to correct the term of United States Patent No. 7,553,828 ("the '828 patent").

2. Specifically, under rules designed to compensate patent applicants for USPTO delays in examining applications and issuing patents, the USPTO calculated that the term of the '828 patent should be extended by 358 days. The USPTO, however, incorrectly calculated that extension when, under its interpretation of the relevant rules, it failed to credit certain delays totaling 345 days. The USPTO's miscalculation thus deprives Paratek of nearly a year of patent

protection. Accordingly, Paratek seeks an additional adjustment of 345 days (equal to the period of delay that the USPTO failed to credit), for a total adjustment of 703 days.

PARTIES

3. The plaintiff, Paratek, is a Boston-based biopharmaceutical company and the owner of the '828 patent. Paratek's principal business is the discovery and commercialization of therapeutics (such as novel antibiotics) for treating infections and serious diseases. Paratek's headquarters are located at 75 Kneeland Street, Boston, MA 02111.

4. The defendant, the Honorable David Kappos, is Under Secretary of Commerce for Intellectual Property and Director of the USTPO. The USPTO, under the supervision of Under Secretary Kappos's predecessor, Acting Under Secretary and Acting Director John Doll, incorrectly calculated the term adjustment for the '828 patent. The USPTO Director is designated by statute, 35 U.S.C. § 154(b)(4), as the named defendant in patent term adjustment litigation. Accordingly, Under Secretary Kappos is being sued in his official capacity as USPTO Director. The USPTO's primary address is the Madison Building, 600 Dulany Street, Alexandria, VA 22314. Legal papers, however, are sent to Office of the General Counsel, PO Box 15667, Arlington, VA 22215.

JURISDICTION

5. This Court has jurisdiction over this action and is authorized to grant the requested relief in accordance with 28 U.S.C. §§ 1331 (federal question), 1338(a) (jurisdiction in patent cases) and 1361 (actions to compel performance by U.S. officials); 35 U.S.C. § 154(b)(4) (patent term adjustment actions); and 5 U.S.C. §§ 701-706 (judicial review of agency actions).

6. Venue in this district is mandated by 35 U.S.C. § 154(b)(4).

7. Paratek has filed its complaint within 180 days of the grant of the '828 patent, as specified in § 154(b)(4).

BACKGROUND FACTS

A. The '828 Patent

8. The '828 patent, entitled "9-Aminomethyl Substituted Minocycline Compounds," issued on June 30, 2009. The inventors are Mark Nelson and several other Paratek scientists. The '828 patent is directed to certain antibiotic compounds and drugs used, for example, in treating infections and other ailments. The '828 patent represents a breakthrough in treating bacteria that have become resistant to tetracycline-based antibiotics and in treating a variety of other serious health concerns.

9. Paratek owns the '828 patent via assignments from the inventors, which are recorded in the USPTO. A copy of the patent is attached as Exhibit A.

B. Prosecution of the Application Resulting in the '828 Patent

10. The '828 patent results from an application (Serial No. 10/786,881) filed in the USPTO on February 24, 2004. Paratek, as the assignee and acting on behalf of the named inventors, prosecuted this application through the USPTO's examination process.

11. As detailed below, the USPTO is required to examine a patent application and issue a first office action within fourteen months after the application is filed.[1] In this case, however, the USPTO examiner did not issue the first office action (a relatively minor "restriction requirement") until October 11, 2006, two years and eight months after the application was filed and one-and-a-half years after the fourteen-month deadline for examining patents.

[1] An "office action" is the USPTO examiner's official written response to the merits of a patent application or its compliance with various technical requirements and formalities. An office action may include anything from a notice of allowance to a preliminary rejection of the application based on patentability concerns.

12. Paratek promptly responded to this first office action on November 10, 2006. After another round of correspondence between Paratek and the USPTO from December 2006 to May 2007 (*i.e.*, another office action and response), the USPTO examiner issued a final office action on August 6, 2007, rejecting the pending application.

13. Paratek filed a notice of appeal to the Board of Patent Appeals and Interferences ("BPAI") on February 5, 2008. (The appeal became moot when, on December 1, 2008, the USPTO examiner issued a new, non-final office action.) Also, on February 26, 2008, Paratek filed a request for continued examination of its application. At the same time, Paratek filed a response to the final office action from the previous August.

14. In response to Paratek's filings, the USPTO examiner issued a non-final office action on June 13, 2008. Paratek responded just two weeks later, on June 27, 2008.

15. Although, as detailed below, the USPTO must answer applicants' responses to office actions within four months, the USPTO examiner in this case took more than five months to respond to Paratek's June 27th filing. Specifically, on December 1, 2008, the examiner issued yet another office action. Paratek promptly responded on December 16, 2008.

16. Under the patent term adjustment statute, the USPTO may not keep an application pending for more than three years. In this case, however, the '828 patent remained pending for over five years. On March 11, 2009, the USPTO notified Paratek that the patent application was finally allowed and that a patent would be issued in due course. On June 30, 2009, the USPTO issued what is now the '828 patent, over two years past the three-year pendency deadline

C. The USPTO's Adjustment of the Patent Term

17. Under the patent term adjustment provision of the Patent Act, 35 U.S.C. § 154(b), and as further explained in this Court's opinion in *Wyeth v. Dudas*, 580 F. Supp. 2d 138 (D.D.C.

2008), a patentee is entitled to a patent term extension of one day for every day that the USPTO delays examination of the patent application or issuance of the resulting patent. As explained in *Wyeth*, the limited term of a patent runs from the date the application is filed, not from the date the patent issues, and thus "some of the effective term of a patent is consumed by the time it takes to prosecute the application." *Id.* at 139. The patent term adjustment provision, therefore, is used to "mitigate the damage that bureaucracy can do to inventors." *Id.*

18. To ensure speedier examination of patent applications so that patentees are not prejudiced by USPTO delays, federal law and regulations require that the USPTO complete certain phases of the examination process within certain prescribed times. These time limits are set forth in 35 U.S.C. § 154(b)(1) *et seq*, and 37 C.F.R. § 1.703(a) *et seq*.. For example, as prefaced above, the patent applicant is entitled to a first office action within fourteen months of filing the application. For each day past these deadlines that the USPTO delays in taking the required action, the patentee is entitled to an extra day of the resulting patent's term. Any delay caused by the patent applicant is subtracted from this term adjustment.

19. For purposes of this case, two categories of delays are relevant to the term adjustment calculations. As further detailed in *Wyeth*, so-called "A delays" (*i.e.*, those listed under § 154(b)(1)(A)) include, for example, delays past the fourteen-month window for issuing a first office action and delays past the four-month window for responding to an applicant's correspondence. So-called "B delays" (as enumerated in § 154(b) (1)(B)) include the delay in keeping patents pending for more than three years.

20. Under this statutory scheme, after the USPTO allows a patent application, the Director must calculate the period of delay attributable to the USPTO and adjust the patent term

accordingly. The patentee then has an opportunity to seek correction of the term adjustment via a request for reconsideration filed in the USPTO.

21. The Director calculated that 358 days of USPTO delay should be added to the term of the '828 patent. This determination is shown on the face of the '828 patent. Paratek, however, determined that the Director has under-counted the delay. Thus, on August 27, 2009, Paratek petitioned the USPTO to correct the patent term and sought reconsideration of the Director's calculations. On December 7, 2009, the USPTO denied Paratek's request. *See* **Exhibit B**, Decision on Request for Reconsideration of Patent Term Adjustment.

22. The USPTO's delay was actually **703 days**, as seen in the following calculations:

a. An "A delay" of **535 days** for failing to examine the patent application and issue the first office action within fourteen months of the application's filing. Paratek filed its patent application on February 24, 2004. Thus, the first office action was due fourteen months later, on April 24, 2005. The USPTO examiner, however, did not examine the patent and issue the first office action under October 11, 2006, which is 535 days after the fourteen-month deadline.

b. An "A delay" of **35 days** for failing to respond to Paratek's reply to an office action within four months. Specifically, Paratek responded to an office action on June 27, 2008. The four-month window for answering this response was thus October 27, 2008. But the examiner did not respond and issue another office action until December 1, 2008--35 days after the deadline.

c. A "B delay" of **345 days** for keeping the patent pending for more than three years. Specifically, the three-year pendency period expired on February 24, 2007, but the USPTO did not issue the patent until June 30, 2009--two years and five months (856 days) after the deadline. Under the statutory scheme, however, the time consumed by appeals and continued examination is excluded from the term adjustment calculations. In this case, Paratek filed a notice of appeal with the BPAI on February 5, 2008, and, on February 26, 2008, requested continued examination after the final office action. The period consumed by the appeal and continued examination was 511 days, from February 5, 2008, until June 30, 2009, when the '828 patent issued. Thus, this 511 days is subtracted from the overall 856-day period to give an adjusted delay of 345 days. Another way to view this result is that the USPTO's B delay ran from February 25, 2007 (the day after the three-year pendency limit) to February 5, 2008, when Paratek filed its notice of appeal. Again, this period is 345 days.

d. The total USPTO delays, minus the period of appeal and continued examination, was thus 915 days (535 + 35 + 345 = 915).

e. Paratek, however, took extra time to respond to certain office actions during the course of the examination process. Under the statutory scheme, any delay by the applicant is subtracted from the total USPTO delay. Thus, the total time attributable to USPTO delay is **703 days** (915 USPTO delay days - 212 Paratek delay days = 703 days).

23. The reason for the discrepancy between Paratek's and the Director's calculations appears to be that the Director mistakenly treated 345 days of the "B delay" (*i.e.*, the period past the initial three-year patent pendency period) as overlapping with the "A delay," even though those periods did not overlap. In particular, the first A delay (the delay after the fourteen-month deadline for issuing the first office action) occurred from April 24, 2005, to October 11, 2006. The B delay, however, did not start until the third anniversary of the application filing date, on February 24, 2007. Accordingly, these days could not overlap. The Director, however, appears to have treated the "B delay" as running from the date of the application's filing rather than from the third anniversary of the application's filing. As a result, contrary to the correct implementation of the patent term adjustment law, the Director has decided that the A and B delay period overlap and has thus not counted a substantial portion of the delay. Put another way, the Director failed to account for the 345-day "B delay" altogether.

COUNT I
PATENT TERM ADJUSTMENT APPEAL UNDER 35 U.S.C. § 154(b)(4)

24. Paratek incorporates by reference the allegations of the preceding paragraphs.

25. As detailed above, the Director incorrectly calculated the period of the USPTO's delay when he adjusted the term of the '828 patent. Paratek is entitled to a patent term adjustment of 703 days. The Director, however, added only 358 days to the term.

26. This adjustment under-counts the period of delay by 345 days and thus deprives Paratek of nearly a year of valuable patent protection. In particular, the Director apparently failed to credit the 345-day period that the USPTO kept the patent pending after the statutory three-year pendency limit.

27. The Director's failure to account for this period conflicts with the correct method of calculating patent term adjustments laid out in this Court's opinion in *Wyeth v. Dudas*, 580 F. Supp. 2d 138 (D.D.C. 2008).

28. The Director's determination that the '828 patent is entitled to only 358 days of patent term adjustment, rather than the full 703 days of USPTO delay, is arbitrary, capricious, an abuse of discretion, otherwise not in compliance with the law, and unsupported by substantial evidence. The Director's determination also exceeded his authority, statutory jurisdiction, or other legal limitations.

ACCORDINGLY, Paratek Pharmaceuticals, Inc., respectfully requests the following relief:

A. A judgment for Paratek that the Director incorrectly adjusted the term of the '828 patent;

B. An order requiring the Director to adjust the term of the '828 patent by an additional 345 days, such that the corrected adjustment is 703 days added to the term of the '828 patent.

C. Such further relief as this Court determines to be just and proper.

Dated: December 28, 2009

Respectfully submitted,

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EXHIBIT A


US007553828B2

(12) **United States Patent**
Nelson et al.

(10) **Patent No.: US 7,553,828 B2**
(45) **Date of Patent: *Jun. 30, 2009**

(54) **9-AMINOMETHYL SUBSTITUTED MINOCYCLINE COMPOUNDS**

(75) Inventors: **Mark L. Nelson**, Norfolk, MA (US); **Roger Frechette**, Reading, MA (US); **Mohamed Y. Ismail**, Bedford, MA (US); **Laura Honeyman**, Roslindale, MA (US); **Todd Bowser**, Charlton, MA (US); **Beena Bhatia**, Arlington, MA (US)

(73) Assignee: **Paratek Pharmaceuticals, Inc.**, Boston, MA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 358 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/786,881**

(22) Filed: **Feb. 24, 2004**

(65) **Prior Publication Data**

US 2005/0026876 A1 Feb. 3, 2005

Related U.S. Application Data

(63) Continuation of application No. 10/412,656, filed on Apr. 10, 2003, now abandoned, which is a continuation-in-part of application No. 10/384,855, filed on Mar. 10, 2003, now abandoned, said application No. 10/412,656 is a continuation-in-part of application No. 09/895,857, filed on Jun. 29, 2001, now Pat. No. 6,846,939.

(60) Provisional application No. 60/395,495, filed on Jul. 12, 2002, provisional application No. 60/362,654, filed on Mar. 8, 2002, provisional application No. 60/275,621, filed on Mar. 13, 2001.

(51) **Int. Cl.**
A61K 31/65 (2006.01)
C07C 50/22 (2006.01)

(52) **U.S. Cl.** **514/152**; 552/205

(58) **Field of Classification Search** 552/205, 552/203, 206; 514/152
See application file for complete search history.

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Primary Examiner—Sabiha N. Qazi
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(57) **ABSTRACT**

The present invention pertains, at least in part, to novel 9-substituted minocycline compounds. These minocycline compounds can be used to treat numerous tetracycline compound-responsive states, such as bacterial infections and neoplasms, as well as other known applications for minocycline and minocycline compounds in general, such as blocking tetracycline efflux and modulation of gene expression.

4 Claims, No Drawings

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9-AMINOMETHYL SUBSTITUTED MINOCYCLINE COMPOUNDS

RELATED APPLICATIONS

This application claims priority to U.S. patent application Ser. No. 10/412,656, filed on Apr. 10, 2003, which claims priority to Ser. No. 10/384,855, filed on Mar. 10, 2003, which claims priority to U.S. Provisional Patent Application Ser. No. 60/395,495, filed on Jul. 12, 2002; and U.S. Provisional Patent Application Ser. No. 60/362,654, filed Mar. 8, 2002. U.S. patent application Ser. No. 10/412,656 also claims priority to U.S. patent application Ser. No. 09/895,857, filed on Jun. 29, 2001, which claims priority to U.S. Patent Application Ser. No. 60/275,621, filed on Mar. 13, 2001. The entire contents of each of the aforementioned applications are incorporated herein by reference.

BACKGROUND OF THE INVENTION

The development of the tetracycline antibiotics was the direct result of a systematic screening of soil specimens collected from many parts of the world for evidence of microorganisms capable of producing bacteriocidal and/or bacteriostatic compositions. The first of these novel compounds was introduced in 1948 under the name chlortetracycline. Two years later, oxytetracycline became available. The elucidation of the chemical structure of these compounds confirmed their similarity and furnished the analytical basis for the production of a third member of this group in 1952, tetracycline. A new family of minocycline compounds, without the ring-attached methyl group present in earlier tetracyclines, was prepared in 1957 and became publicly available in 1967; and minocycline was in use by 1972.

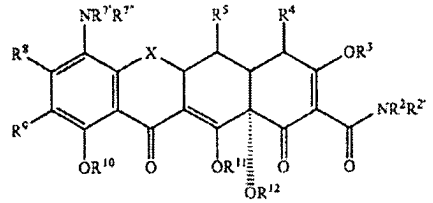
Recently, research efforts have focused on developing new tetracycline antibiotic compositions effective under varying therapeutic conditions and routes of administration. New tetracycline analogues have also been investigated which may prove to be equal to or more effective than the originally introduced minocycline compounds. Examples include U.S. Pat. Nos. 2,980,584; 2,990,331; 3,062,717; 3,165,531; 3,454,697; 3,557,280; 3,674,859; 3,957,980; 4,018,889; 4,024,272; and 4,126,680. These patents are representative of the range of pharmaceutically active tetracycline and tetracycline analogue compositions.

Historically, soon after their initial development and introduction, the tetracyclines were found to be highly effective pharmacologically against rickettsiae; a number of gram-positive and gram-negative bacteria; and the agents responsible for lymphogranuloma venereum, inclusion conjunctivitis, and psittacosis. Hence, tetracyclines became known as "broad spectrum" antibiotics. With the subsequent establishment of their in vitro antimicrobial activity, effectiveness in experimental infections, and pharmacological properties, the tetracyclines as a class rapidly became widely used for therapeutic purposes. However, this widespread use of tetracyclines for both major and minor illnesses and diseases led directly to the emergence of resistance to these antibiotics even among highly susceptible bacterial species both commensal and pathogenic (e.g., *pneumococci* and *Salmonella*). The rise of tetracycline-resistant organisms has resulted in a general decline in use of tetracyclines and tetracycline analogue compositions as antibiotics of choice.

SUMMARY OF THE INVENTION

The invention pertains, at least in part, to compounds of formula I:

(I)



wherein:

X is CHC($R^{13}Y'Y$), $CR^{6'}R^6$, S, NR^6, or O;

R^2, $R^{4'}$, $R^{4''}$, $R^{7'}$ and $R^{7''}$ are each hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a pro-drug moiety;

R^4 is $NR^{4'}R^{4''}$, alkyl, alkenyl, alkynyl, aryl, hydroxyl, halogen, or hydrogen;

$R^{2'}$, R^3, R^{10}, R^{11} and R^{12} are each hydrogen or a pro-drug moiety;

R^5 is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

R^6 and $R^{6'}$ are independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^8 is hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

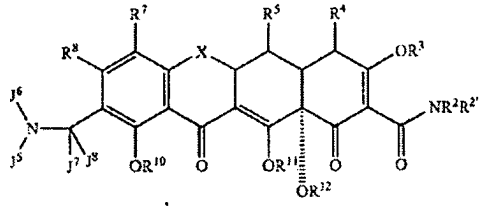
R^9 is aminoalkyl;

R^{13} is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

Y' and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl, and pharmaceutically acceptable salts, esters and prodrugs thereof.

The invention also pertains, at least in part, to compounds of formula (II):

(II)



wherein:

J^5 and J^6 are each independently hydrogen, alkyl, alkenyl, alkynyl, aryl, sulfonyl, acyl, alkoxycarbonyl, alkaminocarbonyl, alkaminothiocarbonyl, substituted thiocarbonyl, substituted carbonyl, alkoxythiocarbonyl, or linked to form a ring;

J^7 and J^8 are each alkyl, halogen, or hydrogen;

X is CHC($R^{13}Y'Y$), $CR^{6'}R^6$, C=$CR^{6'}R^6$, S, NR^6, or O;

R^2, $R^{2'}$, $R^{4'}$, and $R^{4''}$ are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

R^4 is $NR^{4'}R^{4''}$, alkyl, alkenyl, alkynyl, aryl, hydroxyl, halogen, or hydrogen;

$R^{2'}$, R^3, R^{10}, R^{11} and R^{12} are each hydrogen or a pro-drug moiety;

R^5 is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

R^6 and $R^{6'}$ are each independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

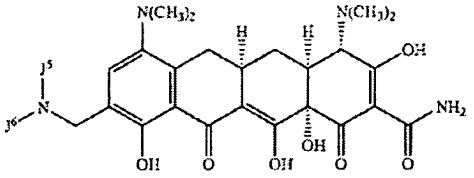
R^7 and R^8 and are each independently hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^{13} is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl; and

Y' and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl, and pharmacentically acceptable salts thereof

A compound of the formula (III):

(III)



wherein

$J^5$is alkyl; and

J^6 is hydrogen, or pharmaceutically acceptable salts, prodrugs and esters thereof.

The invention also pertains to pharmaceutical compositions comprising the compounds of the invention (e.g., compounds of formula (I), (II), (III), or otherwise described herein) and a pharmaceutically acceptable carrier. The invention also pertains to the use of a compound of the invention for the manufacture of a medicament, e.g., a medicament for the treatment of a tetracycline responsive state.

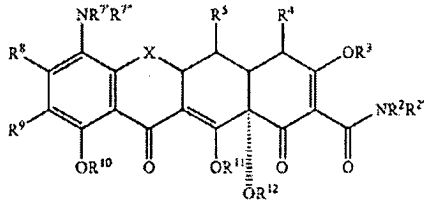
The invention also pertains to methods of using the compounds of the invention to treat subjects suffering from tetracycline compound responsive states.

DETAILED DESCRIPTION OF THE INVENTION

The present invention pertains, at least in part, to novel 9-substituted minocycline compounds. These minocycline compounds can be used to treat numerous tetracycline compound-responsive states, such as bacterial infections and neoplasms, as well as other known applications for minocycline and minocycline compounds in general, such as blocking tetracycline efflux and modulation of gene expression.

The invention pertains, at least in part, to minocycline compounds of Formula I:

(I)



wherein:

X is CHC(R^{13}Y'Y), $CR^{6'}R^6$, S, NR^6, or O;

R^2, $R^{4'}$, $R^{4''}$, R^7 and $R^{7''}$ are each hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl,-heterocyclic, heteroaromatic or a prodrug moiety;

R^4 is $NR^{4'}R^{4''}$, alkyl, alkenyl, alkynyl, aryl, hydroxyl, halogen, or hydrogen;

$R^{2'}$, R^3, R^{10}, R^{11} and R^{12} are each hydrogen or a pro-drug moiety;

R^5 is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

R^6 and $R^{6'}$ are independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^8 is hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or arylalkyl;

R^9 is aminoalkyl;

R^{13} is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

Y' and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl, and pharmaceutically acceptable salts, esters and prodrugs thereof.

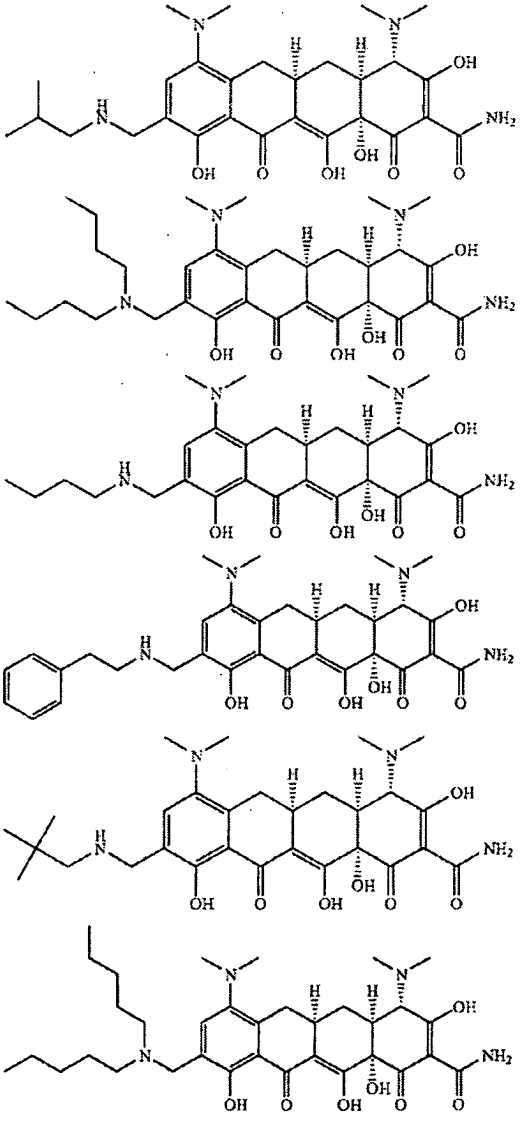
The term minocycline compounds refers to compounds of formulae (I), (II), and (M) above. In an embodiment, the term minocycline compounds include compounds wherein X is $CR^6R^{6'}$; R^2, $R^{2'}$, R^5, R^6, $R^{6'}$, R^8, R^9, R^{10}, R^{11}, and R^{12} are each hydrogen; R^4 is $NR^{4'}R^{4''}$; and $R^{4'}$, $R^{4''}$, R^7, and $R^{7''}$ are each lower alkyl, e.g., methyl. Other compounds of the invention include compounds wherein R^4 is hydrogen.

The invention pertains, at least in part, to compounds of Formula (I) wherein R^9 is aminoalkyl (e.g., aminomethyl, e.g., $—CH_2NR'R''$). Aminoalkyl R^9 groups may be further substituted. Examples of substituents include alkyl, alkenyl, aryl, alkynyl, carbonyl, and acyl groups. Examples of aryl groups include such as, for example substituted or unsubstituted phenyl (e.g., methylenedioxyphenyl or para-perfluoromethoxyphenyl), or heteroaromatic groups which allows the compound of the invention to perform its intended function. Alkyl groups include methyl, ethyl, i-propyl, n-propyl, i-butyl, n-butyl, t-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, etc. Cyclic alkyl groups include groups with one or more rings, such as, for example, cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, etc. In an embodiment, the alkyl R^9 group is 2-cyclopentylethyl.

Examples of substituents of alkyl groups include, for example, halogens (e.g. fluorine, chlorine, bromine, iodine,

etc.), hydroxyl, alkoxy (e.g., methoxy, ethoxy, propoxy, butoxy, pentoxy, perfluoromethoxy, perchloromethoxy, etc.), alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkylaminoacarbonyl, arylalkyl aminocarbonyl, alkenylaminocarbonyl, carboxy, alkylcarbonyl, arylcarbonyl, arylalkylcarbonyl, alkenylcarbonyl, alkoxycarbonyl, silyl, aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonato, phosphinato, cyano, amino, acylamino, amido, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfate, alkylsulfinyl, alkenyl, sulfonato, sulfamoyl, sulfonamido, nitro, alkenyl, cyano, azido, heterocyclyl, alkylaryl, aryl and heteroaryl.

In a further embodiment, the minocycline compound is selected from the group consisting of:



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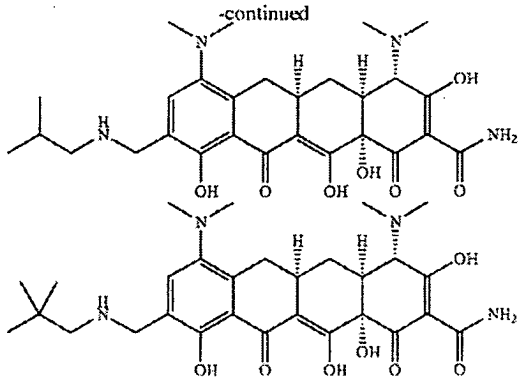


and pharmaceutically acceptable salts, esters and prodrugs thereof.

In another embodiment, the minocycline compound of the invention is a compound wherein R^9 is $—CH_2NR^{9c}C(=Z')ZR^{9a}$, wherein Z is $CR^{9d}R^{9e}$, S, NR^{9b} or O; Z' is NR^{9f}, O or S; and R^{9a}, R^{9b}, R^{9c}, R^{9d}, R^{9e} and R^{9f} are each independently hydrogen, acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety.

In certain embodiments, R^9 is $—CH_2NR^{9c}C(=Z')ZR^{9a}$. Examples of R^{9c} include hydrogen. Z' may be, for example, S, NH, or O. Examples of Z include NR^{9b} (e.g., when R^{9b} is hydrogen, alkyl, etc.), O or S.

Examples of R^{9a} groups include aryl groups such as substituted and unsubstituted phenyl. Examples of possible substituents of aryl R^{9a} groups include, but are not limited to, alkyl (e.g., methyl, ethyl, propyl, butyl, pentyl, hexyl, perfluormethyl, perchloroethyl, etc.), alkenyl, halogen (e.g., fluorine, chlorine, bromine, iodine, etc.), hydroxyl, alkoxy (e.g., methoxy, ethoxy, propoxy, perfluoromethoxy, perchloromethoxy, etc.), alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkylaminoacarbonyl, arylalkyl aminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, arylalkylcarbonyl, alkenylcarbonyl, alkoxycarbonyl, silyl, aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonato, phosphinato, cyano, amino, acylamino, amido, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfate, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, acetyl, alkyl, cyano, azido, heterocyclyl, alkylaryl, aryl and heteroaryl groups.

In certain embodiments, at least one of the substituents of the substituted phenyl is nitro, alkoxy (e.g., methoxy, methylenedioxy, perfluoromethoxy) alkyl (e.g. methyl, ethyl, propyl, butyl, or pentyl), acetyl, halogen (e.g., fluorine, chlorine, bromine, or iodine), or amino (e.g., dialkylamino). In certain embodiments, the alkoxy group is perhalogenated, e.g., perfluoromethoxy.

Examples of aryl R^{9a} groups include, but are not limited to, unsubstituted phenyl, para-nitrophenyl, para-methoxy phenyl, para-perfluoromethoxy phenyl, para-acetyl phenyl, 3,5-methylenedioxyphenyl, 3,5-diperfluoromethyl phenyl, para-bromo phenyl, para-chloro phenyl, and para-fluoro phenyl.

Other examples of aryl R^{9a} groups include substituted and unsubstituted heterocycles (e.g., furanyl, imidazolyl, benzothiophenyl, benzofuranyl, quinolinyl, isoquinolinyl, benzodioxazolyl, benzoxazolyl, benzothiazolyl, benzoimida-

zolyl, methylenedioxyphenyl, indolyl, thienyl, pyrimidyl, pyrazinyl, purinyl, pyrazolyl, pyrolidinyl, oxazolyl, isooxazolyl, naphthridinyl, thiazolyl, isothiazolyl, or deazapurinyl) and substituted and unsubstituted biaryl groups, such as naphthyl and fluorene.

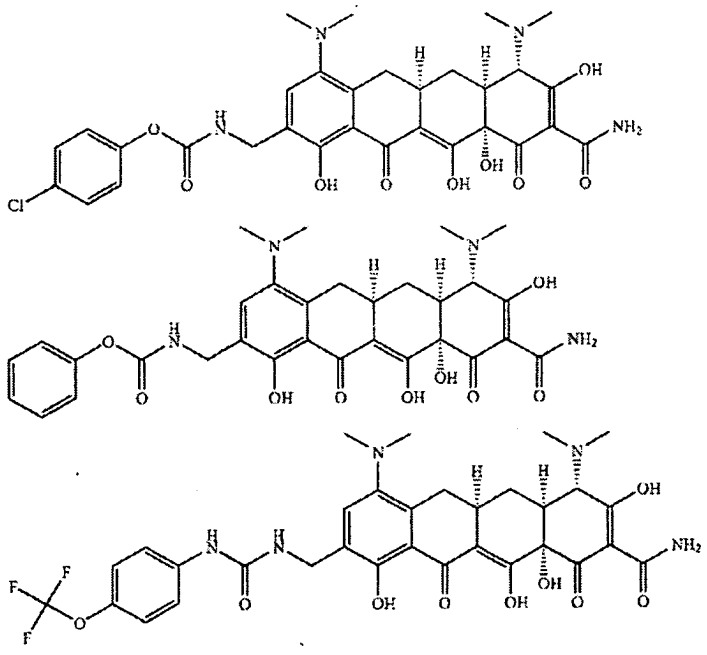
R^{9a} also may be substituted or unsubstituted alkyl, e.g., methyl, ethyl, propyl, butyl, pentyl, etc. Examples of substituents include but are not limited to halogens (e.g., fluorine, bromine, chlorine, iodine, etc.), hydroxyl, alkoxy (e.g., methoxy, ethoxy, propoxy, butoxy, etc.), alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkylaminoacarbonyl, arylalkyl aminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, arylalkylcarbonyl, alkenylcarbonyl, alkoxycarbonyl, silyl, aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonato, phosphinato, cyano, amino, acylamino, amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfate, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, alkenyl, heterocyclyl, alkylaryl, aryl and heteroaryl.

R^{9a} also can be substituted or unsubstituted alkenyl. Examples of substituents for alkenyl R^{9a} groups include those listed above for alkyl R^{9a} groups. Examples of alkenyl R^{9a} groups include pent-1-enyl.

In an embodiment, Z' is NH, Z is NH, and R^{9a} is alkyl.

In a further embodiment, the minocycline compound of the invention does not include compounds wherein R^9 is dimethylmaleimido, when R^9 is dimethylmaleimido or when the compound is described in Martell et al. (*J. Med. Chem.*, (1967, 10(3), 359-3). In another embodiment, the minocycline compounds of the invention do not include compounds wherein R^9 is 4-morpholinylmethyl, when R^7 is hydrogen or when the compound is described in Strel'nokov (*Antibiotiki*, (1965), 10(7), 650-6), Polyak (*Ref Zh., Biol. Khim.* Abstr. No. 6F782), Paikin, M. D. (*Ref Zh., Farmakol, Toksikol.* 1965, Abstr. No. 5.54.323), In another embodiment, the compounds of the invention do not include compounds wherein R^9 is 1-pyrrolidinylmethyl, when R^7 is hydrogen, or compounds otherwise described in Genazzini, E. et al. (*Atti. Soc. Ital. Sci. Vet.* (1964), 18, 175-8, Hajdu, P. *Arzneimittel-Forsch.* (1962), 12, 206-7, *Federal Register*, (1962), 27, 3851, Baldini et al. *Boll. Soc. Ital. Biol. Sper.* (1960), 36, 577-83), Good, W., *Biochim. et Biophys., Acta*, (1962) 56, 359-61; Ritzerfeld, W., *Arzneimittel-Forsch*, (1962), 12. 30-2; Maniar, A. et al., *Ann. Inst. Pasteur*, (1961), 101, 887-97); Garrod. L., *Recenti Progr. Med.* (1962), 32, 3-24; Branceni, *Compt. Rend. Soc. Biol.* (1961), 155, 1469-72, ES 302929. In another embodiment, the compounds of the invention do not include compounds wherein R^9 is $—CH_2NHCH_2C(=O)NH_2$, $—CH_2NHCH(CH_3)C(=O)NH(CH_2)_2OH$, $—CH_2NHCH(CH_3)C(=O)NH_2$, $—CH_2NHCH_2C(=O)NHCH_3$, $—CH_2NHCH_2C(=O)NH(CH_2)_2OH$, or $—CH_2NHCH(C(=O)NH(CH_2)_2)(CH_2)_4NH_2$, or $—CH_2NHCH(C(=O)(CH_2)_4NH_2$, when R^7 is H, or otherwise described in GB921252 or GB 955766.

Examples of minocycline compounds of the invention include those listed in Table 1, as well as the ones listed below:



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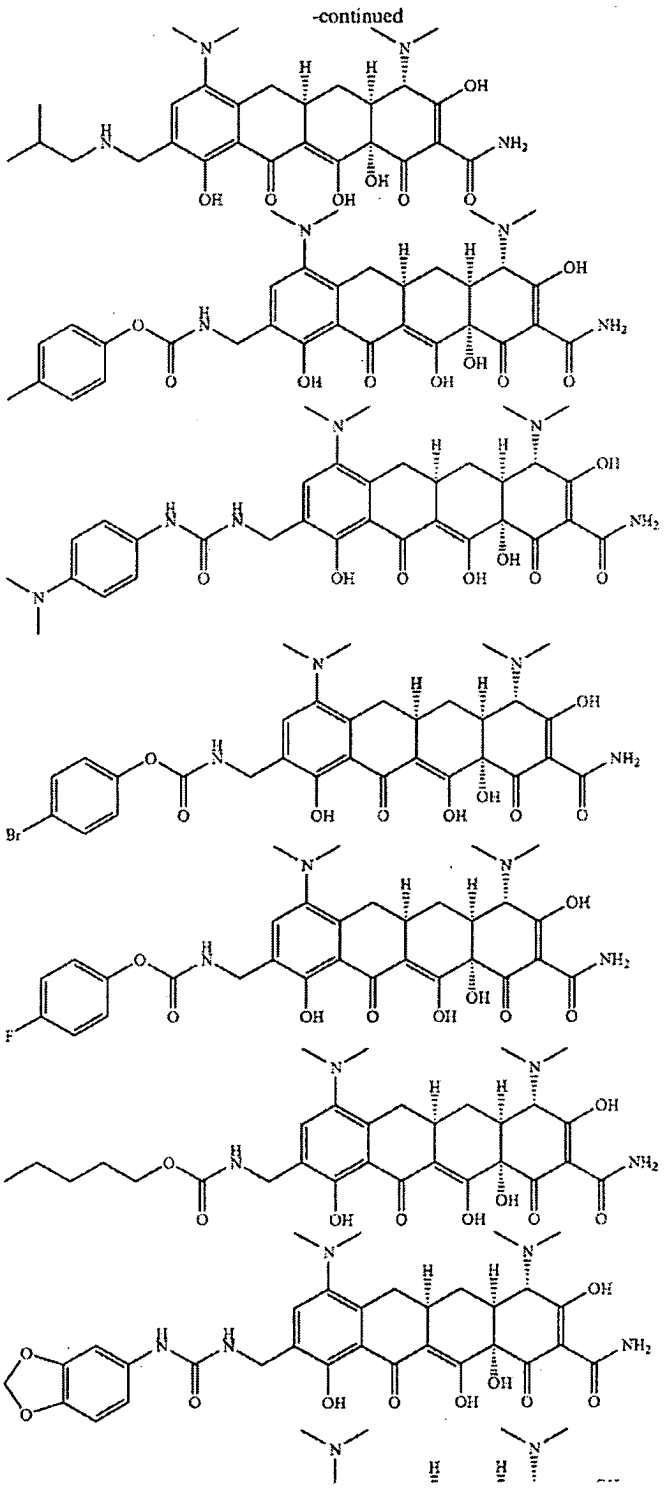
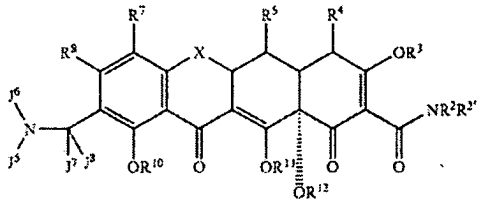


The invention also pertains, at least in part, to minocycline compounds of formula (II):

(II)



wherein:

J^5 and J^6 are each independently hydrogen, alkyl, alkenyl, alkynyl, aryl, sulfonyl, acyl, alkoxycarbonyl, alkaminocarbonyl, alkaminothiocarbonyl, substituted thiocarbonyl, substituted carbonyl, alkoxythiocarbonyl, or linked to form a ring;

$J^7$and $J^8$are each alkyl, halogen, or hydrogen;

X is CHC(R^{13}Y'Y), $CR^{6'}R^6$, C=$CR^{6'}R^6$, S, NR^5, or O;

R^2, $R^{2'}$, $R^{4'}$, and $R^{4''}$ are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

$R^4$is $NR^{4'}R^{4''}$, alkyl, alkenyl, alkynyl, aryl, hydroxyl, halogen, or hydrogen;

$R^{2'}$, R^3, R^{10}, R^{11} and R^{12} are each hydrogen or a pro-drug moiety;

R^5 is hydroxyl, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, alkyl carbonyloxy, or aryl carbonyloxy;

R^6 and $R^{6'}$ are each independently hydrogen, methylene, absent, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^8 and R^7 are each independently hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

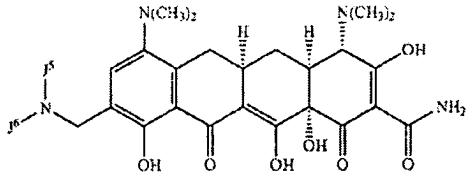
R^{13} is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl; and

Y' and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl, and pharmaceutically acceptable salts thereof.

In one embodiment, $R^{4'}$ and $R^{4''}$ are each methyl and R^5 is hydrogen. In another further embodiment, J^7 and J^8 are hydrogen. In another embodiment, J^5 is substituted or unsubstituted alkyl, e.g., branched or straight chain alkyl. In another embodiment, J^5 is methyl, ethyl, propyl, pentyl, hexyl, octyl, etc. In a further embodiment, J^5 is n-pentyl. In another further embodiment, J^6 is hydrogen.

A compound of the formula (III):

(III)



wherein

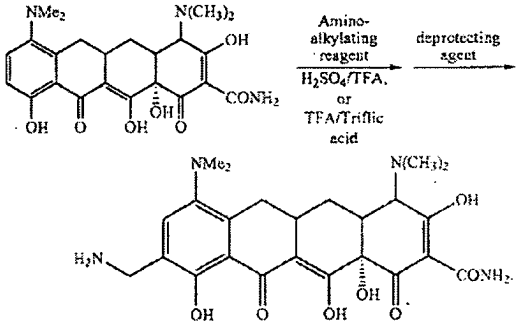
J^5 is alkyl; and

J^6 is hydrogen, or pharmaceutically acceptable salts, prodrugs and esters thereof.

In a further embodiment, J^5 is pentyl, e.g., n-pentyl, and J^6 is hydrogen.

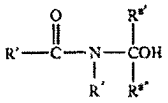
The compounds of this invention can be synthesized using the methods described in Schemes 1-7, in combination with methods known in the art. Scheme 1 depicts the reaction of sancycline with an aminoalkylating reagent under appropriate conditions such that an aminoalkyl minocycline compound is formed.

Scheme 1



Examples of aminoalkylating reagents, include, but are not limited to, compounds of the formula (IV):

(IV)



wherein

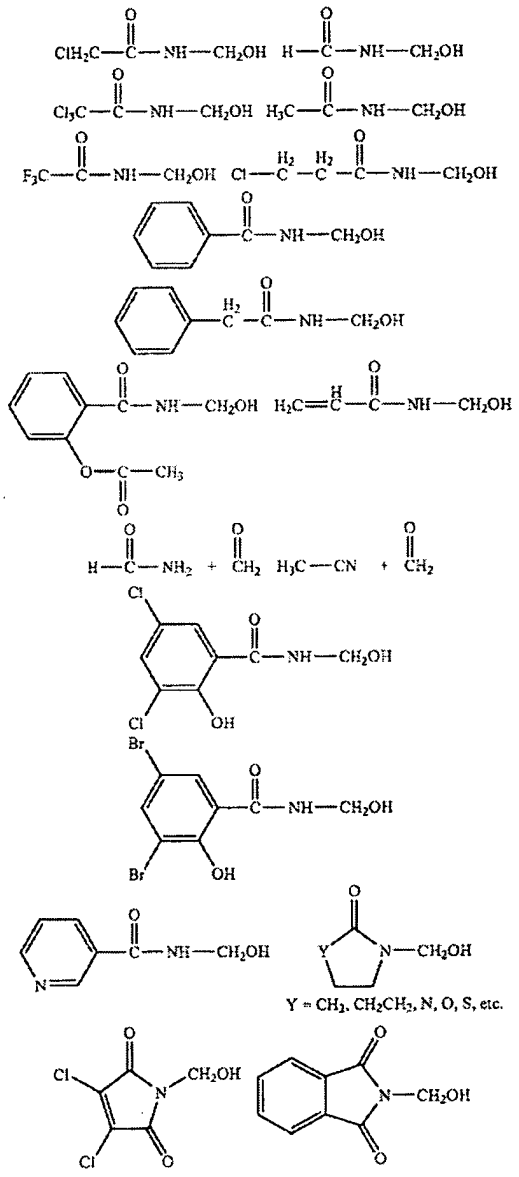
$R^{a'}$ and $R^{a''}$ are each independently hydrogen or halogen;

R' is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, or halogen; and

R" is hydrogen or optionally linked to R' to form a 4-8 membered ring. The ring may be optionally substituted, e.g., with halogens and may comprise carbons and/or heteroatoms such as oxygen, nitrogen, and sulfur. R' may be further substituted with any substituent which does not prevent the reagent from reacting with the tetracycline compound of the invention, under the appropriate conditions. In another further embodiment, R' is alkyl, e.g., unsubstituted or substituted (e.g., with halogens, e.g., chlorine, fluorine, bromine, iodine, etc.). In another embodiment, R' is aryl, e.g., phenyl, e.g.,

unsubstituted or substituted (e.g., with halogens (e.g., chlorine, bromine, fluorine, etc.), hydroxy, alkoxy, esters, amino, etc.). In another embodiment, $R^{a'}$ and $R^{a''}$ are each hydrogen. Other examples of aminoalkylating reagents include N-hydroxymethylphthalimide.

Examples of amino-alkylating reagents include, but are not limited to:

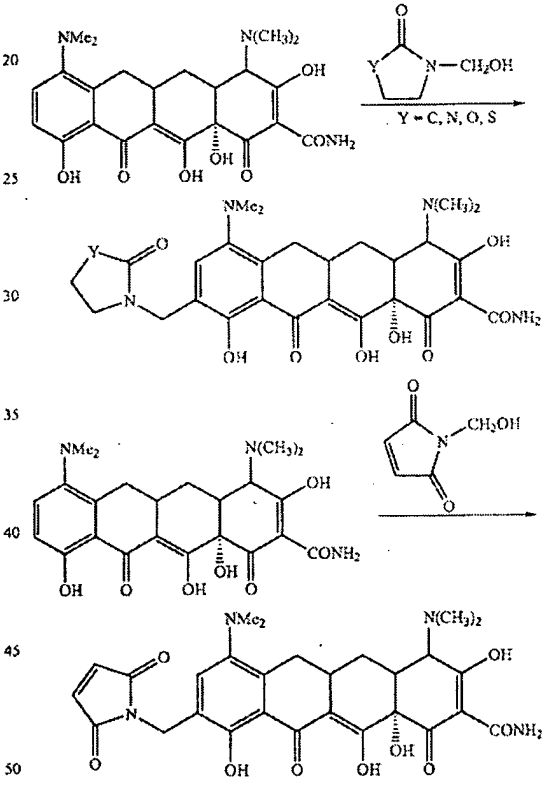


Y = CH_2, CH_2CH_2, N, O, S, etc.

The term "appropriate conditions" include those conditions under which the aminoalkylating reagent and the tetracycline compound interact such that an aminoalkyl tetracycline compound is formed. The appropriate conditions may comprise treating the tetracycline compound with an acid prior to, or concurrently with the addition of the aminoalkylating reagent to the reaction mixture. Examples of acids which maybe used alone or in combination include acids known in the art, as well as, sulfuric acid, hydrofluoric acid (HF), methanesulfonic acid, trifluoromethane sulfonic acid, hydrochloric acid, hydrochloric acid in aqueous ethanol, acetic acid, methanesulfonic acid, and trifluoroacetic acid (TFA). In a further embodiment, appropriate conditions may also comprise treating the resulting tetracycline compound with a reaction quenching agent (e.g., water).

Scheme 2 shows two aminoalkylations of a minocycline compound with aminoalkylating reagents which comprise a 5 membered ring. Similar reactions can be also be carried out using reagents, with, for example, 6- or 7-membered rings.

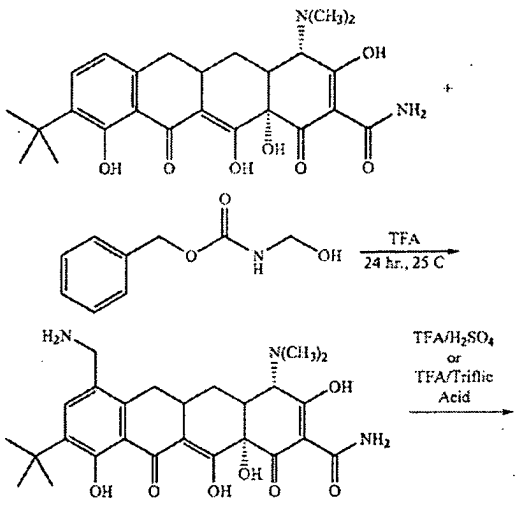
Scheme 2



Y = C, N, O, S

As shown in Scheme 3 below, the synthesis of 7-monosubstituted aminomethyl tetracyclines may be synthesized using protecting groups (i.e. the 9-t-butyl protecting group) to be cleaved using art recognized techniques, such as acid. Examples of acids which can be used include, but are not limited to, HF, trifluoroacetic acid (TFA), H_2SO_4 and mixtures thereof. In this way, regioselective aminomethylation at position 7 is achieved.

Scheme 3



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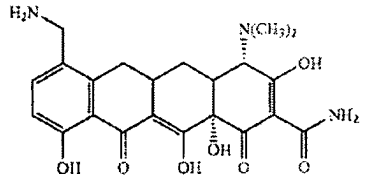
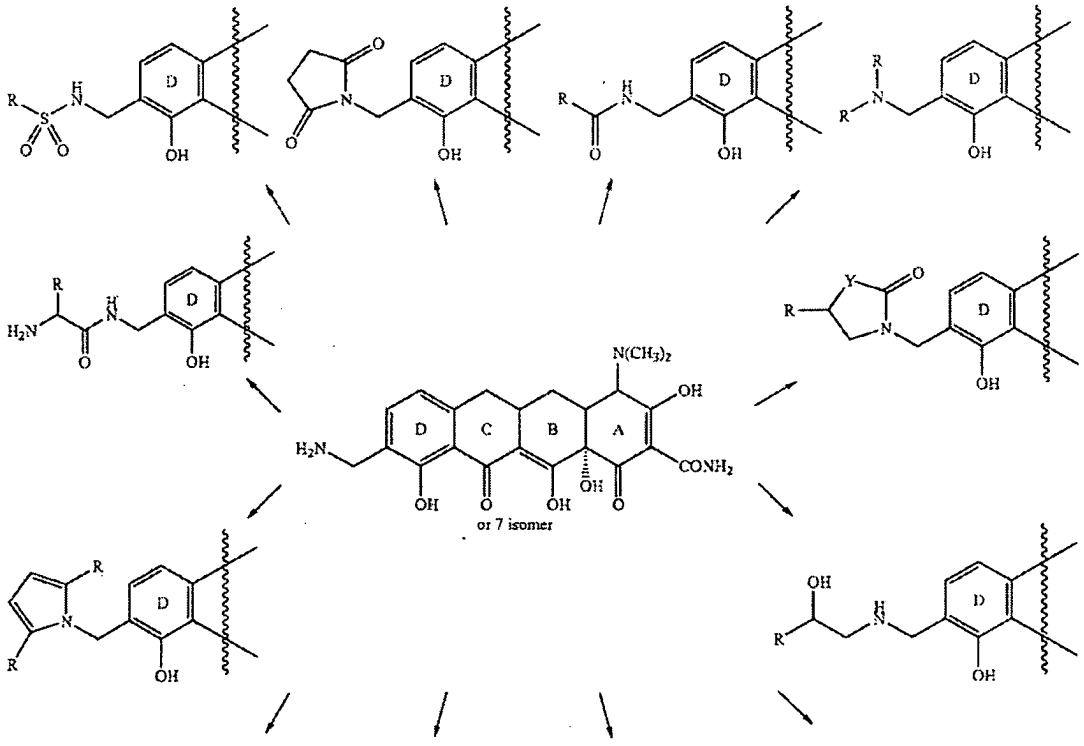


In a further embodiment, the appropriate conditions may further comprise treating the reaction mixture (which may comprise an intermediate aminoalkyl minocycline compound) with a derivatizing agent under secondary appropriate conditions such that the desired aminoalkyl minocycline compound is formed. The reactions in Scheme 4 are shown for the 9 position, but the reactions are also applicable to other positions of the minocycline compound. Additional derivatizing agents and secondary appropriate conditions may be found, for example, in the chemical literature. See, for example, R. C. LaRock, *Comprehensive Organic Transformations*, (New York: VCH Publishers, Inc., 1989) and references cited therein. Any reagent that can react with a primary amine to form a new compound is possible. Examples of some of the diverse structures are shown in Scheme 4 below.

Scheme 4



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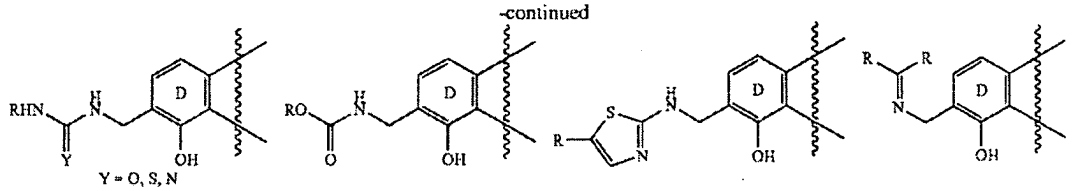
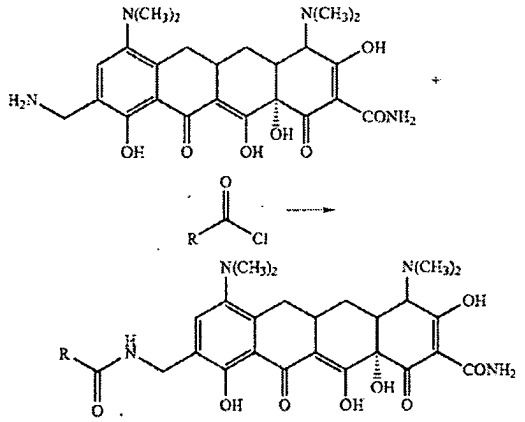


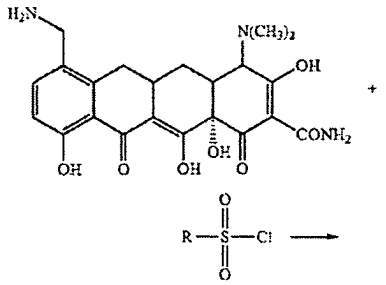
For example, in Scheme 5, an acid chloride derivatizing agent is added to the reaction mixture to form the desired amide aminoalkyl minocycline compound (*J. Am. Chem Soc.* 71, 2215 (1949); *J. Am. Chem. Soc.* 108, 1039 (1986); *Org. Syn. Coll. Vol.* 4, 339 (1963); *Org. Syn. Coll. Vol.* 5, 387 (1973)).

Scheme 5



Scheme 6 depicts the reaction of an intermediate aminoalkyl minocycline compound with an appropriate sulfonyl chloride derivatizing agent, such that the desired sulfonamide aminoalkyl compound is formed (*Org. Syn. Coll. Vol.* 5, 736, 758 (1973)).

Scheme 6



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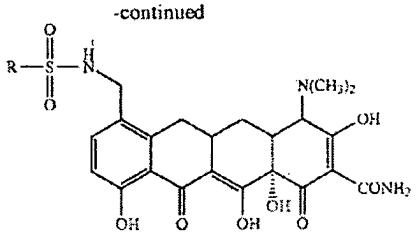
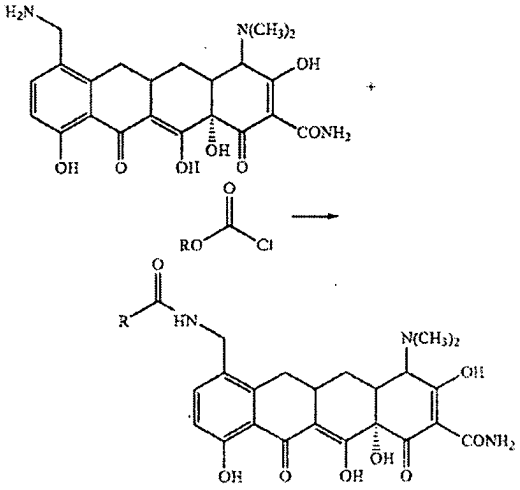


Scheme 7 depicts the reaction of a derivatizing agent with an aminoalkyl tetracycline intermediate to form the resulting carbamate aminoalkyl minocycline compound.

Scheme 7



The term "alkyl" includes saturated aliphatic groups, including straight-chain alkyl groups (e.g., methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, etc.), branched-chain alkyl groups (isopropyl, tert-butyl, isobutyl, etc.), cycloalkyl (alicyclic) groups (cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl), alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. The term alkyl further includes alkyl groups, which can further include oxygen, nitrogen, sulfur or phosphorous atoms replacing one or more carbons of the hydrocarbon backbone. In certain embodiments, a straight chain or branched chain alkyl has 6 or fewer carbon atoms in its backbone (e.g., C_1-C_6 for straight chain, C_3-C_6 for branched chain), and more preferably 4 or fewer. Likewise, preferred cycloalkyls have from

3-8 carbon atoms in their ring structure, and more preferably have 5 or 6 carbons in the ring structure. The term C_1-C_6 includes alkyl groups containing 1 to 6 carbon atoms.

Moreover, the term alkyl includes both "unsubstituted alkyls" and "substituted alkyls", the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety. Cycloalkyls can be further substituted, e.g., with the substituents described above. An "alkylaryl" or an "arylalkyl" moiety is an alkyl substituted with an aryl (e.g., phenylmethyl (benzyl)). The term "alkyl" also includes the side chains of natural and unnatural amino acids.

The term "aryl" includes groups, including 5- and 6-membered single-ring aromatic groups that may include from zero to four heteroatoms, for example, benzene, phenyl, pyrrole, furan, thiophene, thiazole, isothiaozole, imidazole, triazole, tetrazole, pyrazole, oxazole, isooxazole, pyridine, pyrazin, pyridazine, and pyrimidine, and the like. Furthermore, the term "aryl" includes multicyclic aryl groups, e.g., tricyclic, bicyclic, e.g., naphthalene, benzoxazole, benzodioxazole, benzothiazole, benzoimidazole, benzothiophene, methylenedioxyphenyl, quinoline, isoquinoline, napthridine, indole, benzofuran, purine, benzofuran, deazapurine, or indolizine. Those aryl groups having heteroatoms in the ring structure may also be referred to as "aryl heterocycles", "heterocycles," "heteroaryls" or "heteroaromatics". The aromatic ring can be substituted at one or more ring positions with such substituents as described above, as for example, halogen, hydroxyl, alkoxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkylaminoacarbonyl, arylalkyl aminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, arylalkylcarbonyl, alkenylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety. Aryl groups can also be fused or bridged with alicyclic or heterocyclic rings which are not aromatic so as to form a polycycle (e.g., tetralin).

The term "alkenyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double bond.

For example, the term "alkenyl" includes straight-chain alkenyl groups (e.g., ethylenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl, etc.), branched-chain alkenyl groups, cycloalkenyl (alicyclic) groups (cyclopropenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl), alkyl or alkenyl substituted cycloalkenyl groups, and cycloalkyl or cycloalkenyl substituted alkenyl groups. The term alkenyl further includes alkenyl groups which include oxygen, nitrogen, sulfur or phosphorous atoms replacing one or more carbons of the hydrocarbon backbone. In certain embodiments, a straight chain or branched chain alkenyl group has 6 or fewer carbon atoms in its backbone (e.g., C_2-C_6 for straight chain, C_3-C_6 for branched chain). Likewise, cycloalkenyl groups may have from 3-8 carbon atoms in their ring structure, and more preferably have 5 or 6 carbons in the ring structure. The term C_2-C_6 includes alkenyl groups containing 2 to 6 carbon atoms.

Moreover, the term alkenyl includes both "unsubstituted alkenyls" and "substituted alkenyls", the latter of which refers to alkenyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkyl groups, alkynyl groups, halogens, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

The term "alkynyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but which contain at least one triple bond.

For example, the term "alkynyl" includes straight-chain alkynyl groups (e.g., ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl, etc.), branched-chain alkynyl groups, and cycloalkyl or cycloalkenyl substituted alkynyl groups. The term alkynyl further includes alkynyl groups which include oxygen, nitrogen, sulfur or phosphorous atoms replacing one or more carbons of the hydrocarbon backbone. In certain embodiments, a straight chain or branched chain alkynyl group has 6 or fewer carbon atoms in its backbone (e.g., C_2-C_6 for straight chain, C_3-C_6 for branched chain). The term C_2-C_6 includes alkynyl groups containing 2 to 6 carbon atoms.

Moreover, the term alkynyl includes both "unsubstituted alkynyls" and "substituted alkynyls", the latter of which refers to alkynyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkyl groups, alkynyl groups, halogens, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

Unless the number of carbons is otherwise specified, "lower alkyl" as used herein means an alkyl group, as defined above, but having from one to five carbon atoms in its backbone structure. "Lower alkenyl" and "lower alkynyl" have chain lengths of, for example, 2-5 carbon atoms.

The term "acyl" includes compounds and moieties which contain the acyl radical (CH_3CO—) or a carbonyl group. The

term "substituted acyl" includes acyl groups where one or more of the hydrogen atoms are replaced by for example, alkyl groups, alkynyl groups, halogens, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

The term "acylamino" includes moieties wherein an acyl moiety is bonded to an amino group. For example, the term includes alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido groups.

The term "aroyl" includes compounds and moieties with an aryl or heteroaromatic moiety bound to a carbonyl group. Examples of aroyl groups include phenylcarboxy, naphthyl carboxy, etc.

The terms "alkoxyalkyl", "alkylaminoalkyl" and "thioalkoxyalkyl" include alkyl groups, as described above, which further include oxygen, nitrogen or sulfur atoms replacing one or more carbons of the hydrocarbon backbone, e.g., oxygen, nitrogen or sulfur atoms.

The term "alkoxy" includes substituted and unsubstituted alkyl, alkenyl, and alkynyl groups covalently linked to an oxygen atom. Examples of alkoxy groups include methoxy, ethoxy, isopropyloxy, propoxy, butoxy, and pentoxy groups. Examples of substituted alkoxy groups include halogenated alkoxy groups. The alkoxy groups can be substituted with groups such as alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moieties. Examples of halogen substituted alkoxy groups include, but are not limited to, fluoromethoxy, difluoromethoxy, trifluoromethoxy, chloromethoxy, dichloromethoxy, trichloromethoxy, etc.

The term "amine" or "amino" includes compounds where a nitrogen atom is covalently bonded to at least one carbon or heteroatom. The term "alkyl amino" includes groups and compounds wherein the nitrogen is bound to at least one additional alkyl group. The term "dialkyl amino" includes groups wherein the nitrogen atom is bound to at least two additional alkyl groups. The term "arylamino" and "diarylamino" include groups wherein the nitrogen is bound to at least one or two aryl groups, respectively. The term "alkylarylamino," "alkylaminoaryl" or "arylaminoalkyl" refers to an amino group which is bound to at least one alkyl group and at least one aryl group. The term "alkaminoalkyl" refers to an alkyl, alkenyl, or alkynyl group bound to a nitrogen atom which is also bound to an alkyl group.

The term "amide" or "aminocarbonyl" includes compounds or moieties which contain a nitrogen atom which is bound to the carbon of a carbonyl or a thiocarbonyl group. The term includes "alkaminocarbonyl" or "alkylaminocarbonyl" groups which include alkyl, alkenyl, aryl or alkynyl groups bound to an amino group bound to a carbonyl group. It includes arylaminocarbonyl groups which include aryl or heteroaryl moieties bound to an amino group which is bound to the carbon of a carbonyl or thiocarbonyl group. The terms "alkylaminocarbonyl," "alkenylaminocarbonyl," "alkynylaminocarbonyl," "arylaminocarbonyl," "alkylcarbonylamino," "alkenylcarbonylamino," "alkynylcarbonylamino," and "arylcarbonylamino" are included in term "amide." Amides also include urea groups (aminocarbonylamino) and carbamates (oxycarbonylamino).

The term "carbonyl" or "carboxy" includes compounds and moieties which contain a carbon connected with a double bond to an oxygen atom. Examples of moieties which contain a carbonyl include aldehydes, ketones, carboxylic acids, amides, esters, anhydrides, etc.

The term "thiocarbonyl" or "thiocarboxy" includes compounds and moieties which contain a carbon connected with a double bond to a sulfur atom.

The term "ether" includes compounds or moieties which contain an oxygen bonded to different carbon atoms or heteroatoms. For example, the term includes "alkoxyalkyl" which refers to an alkyl, alkenyl, or alkynyl group covalently bonded to an oxygen atom which is covalently bonded to another alkyl group.

The term "ester" includes compounds and moieties which contain a carbon or a heteroatom bound to an oxygen atom which is bonded to the carbon of a carbonyl group. The term "ester" includes alkoxycarboxy groups such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, pentoxycarbonyl, etc. The alkyl, alkenyl, or alkynyl groups are as defined above.

The term "thioether" includes compounds and moieties which contain a sulfur atom bonded to two different carbon or hetero atoms. Examples of thioethers include, but are not limited to alkthioalkyls, alkthioalkenyls, and alkthioalkynyls. The term "alkthioalkyls" include compounds with an alkyl, alkenyl, or alkynyl group bonded to a sulfur atom which is bonded to an alkyl group. Similarly, the term "alkthioalkenyls" and alkthioalkynyls" refer to compounds or moieties wherein an alkyl, alkenyl, or alkynyl group is bonded to a sulfur atom which is covalently bonded to an alkynyl group.

The term "hydroxy" or "hydroxyl" includes groups with an —OH or —O⁻.

The term "halogen" includes fluorine, bromine, chlorine, iodine, etc. The term "perhalogenated" generally refers to a moiety wherein all hydrogens are replaced by halogen atoms.

The terms "polycyclyl" or "polycyclic radical" refer to two or more cyclic rings (e.g., cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls) in which two or more carbons are common to two adjoining rings, e.g., the rings are "fused rings". Rings that are joined through non-adjacent atoms are termed "bridged" rings. Each of the rings of the polycycle can be substituted with such substituents as described above, as for example, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkoxycarbonyl, alkylaminoacarbonyl, arylalkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, arylalkyl carbonyl, alkenylcarbonyl, aminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and urcido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trif-

luoromethyl, cyano, azido, heterocyclyl, alkyl, alkylaryl, or an aromatic or heteroaromatic moiety.

The term "heteroatom" includes atoms of any element other than carbon or hydrogen. Preferred heteroatoms are nitrogen, oxygen, sulfur and phosphorus.

The term "prodrug moiety" includes moieties which can be metabolized in vivo to an active group and moieties which may advantageously remain attached in vivo. Preferably, the prodrugs moieties are metabolized in vivo by enzymes, e.g., esterases or by other mechanisms to hydroxyl groups or other advantageous groups. Examples of prodrugs and their uses are well known in the art (See, e.g., Berge et al. (1977) "Pharmaceutical Salts", *J. Pharm. Sci.* 66:1-19). The prodrugs can be prepared in situ during the final isolation and purification of the compounds, or by separately reacting the purified compound with a suitable agent. Hydroxyl groups can be converted into esters via treatment with a carboxylic acid. Examples of prodrug moieties include substituted and unsubstituted, branch or unbranched lower alkyl ester moieties, (e.g., propionoic acid esters), lower alkenyl esters, di-lower alkyl-amino lower-alkyl esters (e.g., dimethylaminoethyl ester), acylamino lower alkyl esters (e.g., acetyloxymethyl ester), acyloxy lower alkyl esters (e.g., pivaloyloxymethyl ester), aryl esters (phenyl ester), aryl-lower alkyl esters (e.g., benzyl ester), substituted (e.g., with methyl, halo, or methoxy substituents) aryl and aryl-lower alkyl esters, amides, lower-alkyl amides, di-lower alkyl amides, and hydroxy amides. Preferred prodrug moieties are propionoic acid esters and acyl esters.

It will be noted that the structure of some of the compounds of this invention includes asymmetric carbon atoms. It is to be understood accordingly that the isomers arising from such asymmetry (e.g., all enantiomers and diastereomers) are included within the scope of this invention, unless indicated otherwise. Such isomers can be obtained in substantially pure form by classical separation techniques and by stereochemically controlled synthesis. Furthermore, the structures and other compounds and moieties discussed in this application also include all tautomers thereof.

The invention also pertains to methods for treating a tetracycline responsive states in subjects, by administering to a subject an effective amount of a compound of the invention (e.g., a compound of Formula (I), (II), (III), or otherwise described herein), such that the tetracycline responsive state is treated.

The language "tetracycline compound responsive state" or "tetracycline responsive state" includes states which can be treated, prevented, or otherwise ameliorated by the administration of a compound of the invention, e.g., a compound of Formula (I), (II), (III) or otherwise described herein. Tetracycline compound responsive states include bacterial, viral, and fugal infections (including those which are resistant to other tetracycline compounds), cancer (e.g., prostate, breast, colon, lung melanoma and lymph cancers and other disorders characterized by unwanted cellular proliferation, including, but not limited to, those described in U.S. Pat. No. 6,100,248), arthritis, osteoporosis, diabetes, cystic fibrosis, neurological disorders and other states for which tetracycline compounds have been found to be active (see, for example, U.S. Pat. Nos. 5,789,395; 5,834,450; 6,277,061 and 5,532,227, each of which is expressly incorporated herein by reference). Compounds of the invention can be used to prevent or control important mammalian and veterinary diseases such as diarrhea, urinary tract infections, infections of skin and skin structure, ear, nose and throat infections, wound infection, mastitis and the like. In addition, methods for treating neoplasms using tetracycline compounds of the invention are also included (van der Bozert et al., *Cancer Res.*, 48:6686-6690 (1988)). In a further embodiment, the tetracycline responsive state is not a bacterial infection. Other tetracycline compound responsive states include, for example, those described in U.S. Ser. No. 10/196,010.

Tetracycline compound responsive states also include inflammatory process associated states (IPAS). The term "inflammatory process associated state" includes states in which inflammation or inflammatory factors (e.g., matrix metalloproteinases (MMPs), nitric oxide (NO), TNF, interleukins, plasma proteins, cellular defense systems, cytokines, lipid metabolites, proteases, toxic radicals, adhesion molecules, etc.) are involved or are present in an area in aberrant amounts, e.g., in amounts which may be advantageous to alter, e.g., to benefit the subject. The inflammatory process is the response of living tissue to damage. The cause of inflammation may be due to physical damage, chemical substances, micro-organisms, tissue necrosis, cancer or other agents. Acute inflammation is short-lasting, lasting only a few days. If it is longer lasting however, then it may be referred to as chronic inflammation.

IPAS's include inflammatory disorders. Inflammatory disorders are generally characterized by heat, redness, swelling, pain and loss of function. Examples of causes of inflammatory disorders include, but are not limited to, microbial infections (e.g., bacterial and fungal infections), physical agents (e.g., burns, radiation, and trauma), chemical agents (e.g., toxins and caustic substances), tissue necrosis and various types of immunologic reactions.

Examples of inflammatory disorders include, but are not limited to, osteoarthritis, rheumatoid arthritis, acute and chronic infections (bacterial and fungal, including diphtheria and pertussis); acute and chronic bronchitis, sinusitis, and upper respiratory infections, including the common cold; acute and chronic gastroenteritis and colitis; acute and chronic cystitis and urethritis; acute and chronic dermatitis; acute and chronic conjunctivitis; acute and chronic serositis (pericarditis, peritonitis, synovitis, pleuritis and tendinitis); uremic pericarditis; acute and chronic cholecystis; acute and chronic vaginitis; acute and chronic uveitis; drug reactions; insect bites; burns (thermal, chemical, and electrical); and sunburn.

Tetracycline compound responsive states also include NO associated states. The term "NO associated state" includes states which involve or are associated with nitric oxide (NO) or inducible nitric oxide synthase (iNOS). NO associated state includes states which are characterized by aberrant amounts of NO and/or iNOS. Preferably, the NO associated state can be treated by administering tetracycline compounds of the invention, e.g., compounds of formula I, II, III, or otherwise described herein. The disorders, diseases and states described in U.S. Pat. Nos. 6,231,894; 6,015,804; 5,919,774; and 5,789,395 are also included as NO associated states. The entire contents of each of these patents are hereby incorporated herein by reference.

Other examples of NO associated states include, but are not limited to, malaria, senescence, diabetes, vascular stroke, neurodegenerative disorders (Alzheimer's disease, Huntington's disease), cardiac disease (reperfusion-associated injury following infarction), juvenile diabetes, inflammatory disorders, osteoarthritis, rheumatoid arthritis, acute and chronic infections (bacterial, viral, and fungal); cystic fibrosis, acute and chronic bronchitis, sinusitis, and respiratory infections, including the common cold; acute and chronic gastroenteritis and colitis; acute and chronic cystitis and urethritis; acute and chronic dermatitis; acute and chronic conjunctivitis; acute and chronic serositis (pericarditis, peritonitis, synovitis, pleu-

ritis and tendinitis); uremic pericarditis; acute and chronic cholecystis; acute and chronic vaginitis; acute and chronic uveitis; drug reactions; insect bites; burns (thermal, chemical, and electrical); and sunburn.

The term "inflammatory process associated state" also includes, in one embodiment, matrix metalloproteinase associated states (MMPAS). MMPAS include states characterized by aberrant amounts of MMPs or MMP activity. These are also include as tetracycline compound responsive states which may be treated using compounds of the invention, e.g., in formula (I), (II), (III) or otherwise described herein.

Examples of matrix metalloproteinase associated states ("MMPAS's") include, but are not limited to, arteriosclerosis, corneal ulceration, emphysema, osteoarthritis, multiple sclerosis (Liedtke et al., *Ann. Neurol.* 1998, 44:35-46; Chandler et al, *J. Neuroimmunol.* 1997, 72:155-71), osteosarcoma, osteomyelitis, bronchiectasis, chronic pulmonary obstructive disease, skin and eye diseases, periodontitis, osteoporosis, rheumatoid arthritis, ulcerative colitis, inflammatory disorders, tumor growth and invasion (Stetler-Stevenson et al., *Annu. Rev. Cell Biol.* 1993, 9:541-73; Tryggvason et al., *Biochim. Biophys. Acta* 1987, 907:191-217; Li et al., *Mol. Carcinog.* 1998, 22:84-89),metastasis, acute lung injury, stroke, ischemia, diabetes, aortic or vascular aneurysms, skin tissue wounds, dry eye, bone and cartilage degradation (Greenwald et al., *Bone* 1998, 22:33-38; Ryan et al., *Curr. Op. Rheumatol.* 1996, 8;238-247). Other MMPAS include those described in U.S. Pat. Nos. 5,459,135; 5,321,017; 5,308,839; 5,258,371; 4,935,412; 4,704,383, 4,666,897, and RE 34,656, incorporated herein by reference in their entirety.

In another embodiment, the tetracycline compound responsive state is cancer. Examples of cancers which the tetracycline compounds of the invention may be useful to treat include all solid tumors, i.e., carcinomas e.g., adenocarcinomas, and sarcomas. Adenocarcinomas are carcinomas derived from glandular tissue or in which the tumor cells form recognizable glandular structures. Sarcomas broadly include tumors whose cells are embedded in a fibrillar or homogeneous substance like embryonic connective tissue. Examples of carcinomas which may be treated using the methods of the invention include, but are not limited to, carcinomas of the prostate, breast, ovary, testis, lung, colon, and breast. The methods of the invention are not limited to the treatment of these tumor types, but extend to any solid tumor derived from any organ system. Examples of treatable cancers include, but are not limited to, colon cancer, bladder cancer, breast cancer, melanoma, ovarian carcinoma, prostatic carcinoma, lung cancer, and a variety of other cancers as well. The methods of the invention also cause the inhibition of cancer growth in adenocarcinomas, such as, for example, those of the prostate, breast, kidney, ovary, testes, and colon.

In an embodiment, the tetracycline responsive state of the invention is cancer. The invention pertains to a method for treating a subject suffering or at risk of suffering from cancer, by administering an effective amount of a substituted tetracycline compound, such that inhibition cancer cell growth occurs, i.e., cellular proliferation, invasiveness, metastasis, or tumor incidence is decreased, slowed, or stopped. The inhibition may result from inhibition of an inflammatory process, down-regulation of an inflammatory process, some other mechanism, or a combination of mechanisms. Alternatively, the tetracycline compounds may be useful for preventing cancer recurrence, for example, to treat residual cancer following surgical resection or radiation therapy. The tetracycline compounds useful according to the invention are especially advantageous as they are substantially non-toxic compared to other cancer treatments. In a further embodiment, the compounds of the invention are administered in combination with standard cancer therapy, such as, but not limited to, chemotherapy.

The language "in combination with" another therapeutic agent or treatment includes co-administration of the tetracycline compound and with the other therapeutic agent or treatment, administration of the tetracycline compound first, followed by the other therapeutic agent or treatment and administration of the other therapeutic agent or treatment first, followed by the tetracycline compound. The other therapeutic agent may be any agent which is known in the art to treat, prevent, or reduce the symptoms of a tetracycline responsive state. Furthermore, the other therapeutic agent may be any agent of benefit to the patient when administered in combination with the administration of an tetracycline compound. In one embodiment, the cancers treated by methods of the invention include those described in U.S. Pat. Nos. 6,100,248; 5,843,925; 5,837,696; or 5,668,122, incorporated herein by reference in their entirety.

In another embodiment, the tetracycline compound responsive state is diabetes, e.g., juvenile diabetes, diabetes mellitus, diabetes type I, diabetes type II, diabetic ulcers, or other diabetic complications. In a further embodiment, protein glycosylation is not affected by the administration of the tetracycline compounds of the invention. In another embodiment, the tetracycline compound of the invention is administered in combination with standard diabetic therapies, such as, but not limited to insulin therapy. In a further embodiment, the IPAS includes disorders described in U.S. Pat. Nos. 5,929,055; and 5,532,227, incorporated herein by reference in their entirety.

In another embodiment, the tetracycline compound responsive state is a bone mass disorder. Bone mass disorders include disorders where a subjects bones are disorders and states where the formation, repair or remodeling of bone is advantageous. For examples bone mass disorders include osteoporosis (e.g., a decrease in bone strength and density), bone fractures, bone formation associated with surgical procedures (e.g., facial reconstruction), osteogenesis imperfecta (brittle bone disease), hypophosphatasia, Paget's disease, fibrous dysplasia, osteopetrosis, myeloma bone disease, and the depletion of calcium in bone, such as that which is related to primary hyperparathyroidism. Bone mass disorders include all states in which the formation, repair or remodeling of bone is advantageous to the subject as well as all other disorders associated with the bones or skeletal system of a subject which can be treated with the tetracycline compounds of the invention. In a further embodiment, the bone mass disorders include those described in U.S. Pat. Nos. 5,459,135; 5,231,017; 5,998,390; 5,770,588; RE 34,656; 5,308,839; 4,925,833; 3,304,227; and 4,666,897, each of which is hereby incorporated herein by reference in its entirety.

In another embodiment, the tetracycline compound responsive state is acute lung injury. Acute lung injuries include adult respiratory distress syndrome (ARDS), post-pump syndrome (PPS), and trauma. Trauma includes any injury to living tissue caused by an extrinsic agent or event. Examples of trauma include, but are not limited to, crush injuries, contact with a hard surface, or cutting or other damage to the lungs.

The invention also pertains to a method for treating acute lung injury by administering a tetracycline compound of the invention.

The tetracycline responsive states of the invention also include chronic lung disorders. The invention pertains to methods for treating chronic lung disorders by administering a tetracycline compound, such as those described herein. The

method includes administering to a subject an effective amount of a substituted tetracycline compound such that the chronic lung disorder is treated. Examples of chronic lung disorders include, but are not limited, to asthma, cystic fibrosis, and emphysema. In a further embodiment, the tetracycline compounds of the invention used to treat acute and/or chronic lung disorders such as those described in U.S. Pat. Nos. 5,977,091; 6,043,231; 5,523,297; and 5,773,430, each of which is hereby incorporated herein by reference in its entirety.

In yet another embodiment, the tetracycline compound responsive state is ischemia, stroke, or ischemic stroke. The invention also pertains to a method for treating ischemia, stroke, or ischemic stroke by administering an effective amount of a substituted tetracycline compound of the invention. In a further embodiment, the compounds of the invention are used to treat such disorders as described in U.S. Pat. No. 6,231,894; 5,773,430; 5,919,775 or 5,789,395, incorporated herein by reference.

In another embodiment, the tetracycline compound responsive state is a skin wound. The invention also pertains, at least in part, to a method for improving the healing response of the epithelialized tissue (e.g., skin, mucosae) to acute traumatic injury (e.g., cut, burn, scrape, etc.). The method may include using a tetracycline compound of the invention (which may or may not have antibacterial activity) to improve the capacity of the epithelialized tissue to heal acute wounds. The method may increase the rate of collagen accumulation of the healing tissue. The method may also decrease the proteolytic activity in the epithelialized tissue by decreasing the collagenolytic and/or gelatinolytic activity of MMPs. In a further embodiment, the tetracycline compound of the invention is administered to the surface of the skin (e.g., topically). In a further embodiment, the tetracycline compound of the invention is used to treat a skin wound, and other such disorders as described in, for example, U.S. Pat. Nos. 5,827,840; 4,704,383; 4,935,412; 5,258,371; 5,308,8391 5,459,135; 5,532,227; and 6,015,804; each of which is incorporated herein by reference in its entirety.

Examples of tetracycline responsive states also include neurological disorders which include both neuropsychiatric and neurodegenerative disorders, but are not limited to, such as Alzheimer's disease, dementias related to Alzheimer's disease (such as Pick's disease), Parkinson's and other Lewy diffuse body diseases, senile dementia, Huntington's disease, Gilles de la Tourette's syndrome, multiple sclerosis, amyotrophic lateral sclerosis (ALS), progressive supranuclear palsy, epilepsy, and Creutzfeldt-Jakob disease; autonomic function disorders such as hypertension and sleep disorders, and neuropsychiatric disorders, such as depression, schizophrenia, schizoaffective disorder, Korsakoff's psychosis, mania, anxiety disorders, or phobic disorders; learning or memory disorders, e.g., amnesia or age-related memory loss, attention deficit disorder, dysthymic disorder, major depressive disorder, mania, obsessive-compulsive disorder, psychoactive substance use disorders, anxiety, phobias, panic disorder, as well as bipolar affective disorder, e.g., severe bipolar affective (mood) disorder (BP-1), bipolar affective neurological disorders, e.g., migraine and obesity. Further neurological disorders include, for example, those listed in the American Psychiatric Association's Diagnostic and Statistical manual of Mental Disorders (DSM), the most current version of which is incorporated herein by reference in its entirety.

In yet another embodiment, the tetracycline compound responsive state is an aortic or vascular aneurysm in vascular tissue of a subject (e.g., a subject having or at risk of having an aortic or vascular aneurysm, etc.). The tetracycline compound may by effective to reduce the size of the vascular aneurysm or it may be administered to the subject prior to the onset of the vascular aneurysm such that the aneurysm is prevented. In one embodiment, the vascular tissue is an artery, e.g., the aorta, e.g., the abdominal aorta. In a further embodiment, the tetracycline compounds of the invention are used to treat disorders described in U.S. Pat. Nos. 6,043,225 and 5,834,449, incorporated herein by reference in their entirety.

Bacterial infections may be caused by a wide variety of gram positive and gram negative bacteria. The compounds of the invention are useful as antibiotics against organisms which are resistant to other tetracycline compounds. The antibiotic activity of the tetracycline compounds of the invention may be determined using the method discussed in Example 2, or by using the in vitro standard broth dilution method described in Waitz, J. A., *National Commission for Clinical Laboratory Standards*, Document M7-A2, vol. 10, no. 8, pp. 13-20, 2nd edition, Villanova, Pa. (1990).

The tetracycline compounds of the invention may also be used to treat infections traditionally treated with tetracycline compounds such as, for example, rickettsiae; a number of gram-positive and gram-negative bacteria; and the agents responsible for lymphogranuloma venereum, inclusion conjunctivitis, psittacosis. The tetracycline compounds may be used to treat infections of, e.g., *K. pneumoniae, Salmonella, E. hirae, A. baumanii, B. catarrhalis, H. influenzae, P. aeruginosa, E. faecium, E. coli, S. aureus* or *E. faecalis*. In one embodiment, the tetracycline compound is used to treat a bacterial infection that is resistant to other tetracycline antibiotic compounds. The tetracycline compound of the invention may be administered with a pharmaceutically acceptable carrier.

The language "effective amount" of the compound is that amount necessary or sufficient to treat or prevent a tetracycline compound responsive state. The effective amount can vary depending on such factors as the size and weight of the subject, the type of illness, or the particular compound. For example, the choice of the compound can affect what constitutes an "effective amount". One of ordinary skill in the art would be able to study the aforementioned factors and make the determination regarding the effective amount of the tetracycline compound without undue experimentation.

The invention also pertains to methods of treatment against microorganism infections and associated diseases. The methods include administration of an effective amount of one or more minocycline compounds to a subject. The subject can be either a plant or, advantageously, an animal, e.g., a mammal, e.g., a human.

In the therapeutic methods of the invention, one or more minocycline compounds of the invention may be administered alone to a subject, or more typically a compound of the invention will be administered as part of a pharmaceutical composition in mixture with conventional excipient, i.e., pharmaceutically acceptable organic or inorganic carrier substances suitable for parenteral, oral or other desired administration and which do not deleteriously react with the active compounds and are not deleterious to the recipient thereof.

The invention also pertains to pharmaceutical compositions comprising a therapeutically effective amount of a minocycline compound and, optionally, a pharmaceutically acceptable carrier.

The language "pharmaceutically acceptable carrier" includes substances capable of being coadministered with the minocycline compound(s), and which allow both to perform their intended function, e.g., treat or prevent a tetracycline responsive state. Suitable pharmaceutically acceptable carriers include but are not limited to water, salt solutions, alcohol,

vegetable oils, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, petroethral fatty acid esters, hydroxymethyl-cellulose, polyvinylpyrrolidone, etc. The pharmaceutical preparations can be sterilized and if desired mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, colorings, flavorings and/or aromatic substances and the like which do not deleteriously react with the active compounds of the invention.

The minocycline compounds of the invention that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of the minocycline compounds of the invention that are basic in nature are those that form non-toxic acid addition salts, i.e., salts containing pharmaceutically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, acid citrate, tartrate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and palmoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts. Although such salts must be pharmaceutically acceptable for administration to a subject, e.g., a mammal, it is often desirable in practice to initially isolate a minocycline compound of the invention from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent and subsequently convert the latter free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent, such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is readily obtained. The preparation of other minocycline compounds of the invention not specifically described in the foregoing experimental section can be accomplished using combinations of the reactions described above that will be apparent to those skilled in the art.

The preparation of other minocycline compounds of the invention not specifically described in the foregoing experimental section can be accomplished using combinations of the reactions described above that will be apparent to those skilled in the art.

The minocycline compounds of the invention that are acidic in nature are capable of forming a wide variety of base salts. The chemical bases that may be used as reagents to prepare pharmaceutically acceptable base salts of those minocycline compounds of the invention that are acidic in nature are those that form non-toxic base salts with such compounds. Such non-toxic base salts include, but are not limited to those derived from such pharmaceutically acceptable cations such as alkali metal cations (e.g., potassium and sodium) and alkaline earth metal cations (e.g., calcium and magnesium), ammonium or water-soluble amine addition salts such as N-methylglucamine-(meglumine), and the lower alkanolammonium and other base salts of pharmaceutically acceptable organic amines. The pharmaceutically acceptable base addition salts of minocycline compounds of the invention that are acidic in nature may be formed with pharmaceutically acceptable cations by conventional methods. Thus, these salts may be readily prepared by treating the minocycline compound of the invention with an aqueous solution of the desired pharmaceutically acceptable cation and evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, a lower alkyl alcohol solution of the minocycline compound of the invention may be mixed with an alkoxide of the desired metal and the solution subsequently evaporated to dryness.

The preparation of other minocycline compounds of the invention not specifically described in the foregoing experimental section can be accomplished using combinations of the reactions described above that will be apparent to those skilled in the art.

The compounds of the invention and pharmaceutically acceptable salts thereof can be administered via either the oral, parenteral or topical routes. In general, these compounds are most desirably administered in effective dosages, depending upon the weight and condition of the subject being treated and the particular route of administration chosen. Variations may occur depending upon the species of the subject being treated and its individual response to said medicament, as well as on the type of pharmaceutical formulation chosen and the time period and interval at which such administration is carried out.

The pharmaceutical compositions of the invention may be administered alone or in combination with other known compositions for treating tetracycline responsive states in a subject, e.g., a mammal. Preferred mammals include pets (e.g. cats, dogs, ferrets, etc.), farm animals (cows, sheep, pigs, horses, goats, etc.), lab animals (rats, mice, monkeys, etc.), and primates (chimpanzees, humans, gorillas). The language "in combination with" a known composition is intended to include simultaneous administration of the composition of the invention and the known composition, administration of the composition of the invention first, followed by the known composition and administration of the known composition first, followed by the composition of the invention. Any of the therapeutically composition known in the art for treating tetracycline responsive states can be used in the methods of the invention.

The compounds of the invention may be administered alone or in combination with pharmaceutically acceptable carriers or diluents by any of the routes previously mentioned, and the administration may be carried out in single or multiple doses. For example, the novel therapeutic agents of this invention can be administered advantageously in a wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. Moreover, oral pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the therapeutically-effective compounds of this invention are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tablet-

ting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

For parenteral administration (including intraperitoneal, subcutaneous, intravenous, intradermal or intramuscular injection), solutions of a therapeutic compound of the present invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably buffered (preferably pH greater than 8) if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art. For parenteral application, examples of suitable preparations include solutions, preferably oily or aqueous solutions as well as suspensions, emulsions, or implants, including suppositories. Therapeutic compounds may be formulated in sterile form in multiple or single dose formats such as being dispersed in a fluid carrier such as sterile physiological saline or 5% saline dextrose solutions commonly used with injectables.

Additionally, it is also possible to administer the compounds of the present invention topically when treating inflammatory conditions of the skin. Examples of methods of topical administration include transdermal, buccal or sublingual application. For topical applications, therapeutic compounds can be suitably admixed in a pharmacologically inert topical carrier such as a gel, an ointment, a lotion or a cream. Such topical carriers include water, glycerol, alcohol, propylene glycol, fatty alcohols, triglycerides, fatty acid esters, or mineral oils. Other possible topical carriers are liquid petrolatum, isopropylpalmitate, polyethylene glycol, ethanol 95%, polyoxyethylene monolauriate 5% in water, sodium lauryl sulfate 5% in water, and the like. In addition, materials such as anti-oxidants, humectants, viscosity stabilizers and the like also may be added if desired.

For enteral application, particularly suitable are tablets, dragees or capsules having talc and/or carbohydrate carrier binder or the like, the carrier preferably being lactose and/or corn starch and/or potato starch. A syrup, elixir or the like can be used wherein a sweetened vehicle is employed. Sustained release compositions can be formulated including those wherein the active component is protected with differentially degradable coatings, e.g., by microencapsulation, multiple coatings, etc.

In addition to treatment of human subjects, the therapeutic methods of the invention also will have significant veterinary applications, e.g. for treatment of livestock such as cattle, sheep, goats, cows, swine and the like; poultry such as chickens, ducks, geese, turkeys and the like; horses; and pets such as dogs and cats. Also, the compounds of the invention may be used to treat non-animal subjects, such as plants.

It will be appreciated that the actual preferred amounts of active compounds used in a given therapy will vary according to the specific compound being utilized, the particular compositions formulated, the mode of application, the particular site of administration, etc. Optimal administration rates for a given protocol of administration can be readily ascertained by those skilled in the art using conventional dosage determination tests conducted with regard to the foregoing guidelines.

In general, compounds of the invention for treatment can be administered to a subject in dosages used in prior tetracycline therapies. See, for example, the *Physicians' Desk Reference*. For example, a suitable effective dose of one or more compounds of the invention will be in the range of from 0.01 to 100 milligrams per kilogram of body weight of recipient per day, preferably in the range of from 0.1 to 50 milligrams per kilogram body weight of recipient per day, more preferably in the range of 1 to 20 milligrams per kilogram body weight of recipient per day. The desired dose is suitably administered once daily, or several sub-doses, e.g. 2 to 5 sub-doses, are administered at appropriate intervals through the day, or other appropriate schedule.

It will also be understood that normal, conventionally known precautions will be taken regarding the administration of minocyclines generally to ensure their efficacy under normal use circumstances. Especially when employed for therapeutic treatment of humans and animals in vivo, the practitioner should take all sensible precautions to avoid conventionally known contradictions and toxic effects. Thus, the conventionally recognized adverse reactions of gastrointestinal distress and inflammations, the renal toxicity, hypersensitivity reactions, changes in blood, and impairment of absorption through aluminum, calcium, and magnesium ions should be duly considered in the conventional manner.

Furthermore, the invention also pertains to the use of a compound of formula I, II, III, or otherwise described herein for the preparation of a medicament. The medicament may include a pharmaceutically acceptable carrier and the compound is an effective amount, e.g. an effective amount to treat a tetracycline responsive state.

Exemplification of the Invention

Compounds of the invention may be made as described below, with modifications to the procedure below within the skill of those of ordinary skill in the art.

EXAMPLE 1

Synthesis of 9-Aminomethyl Minocycline and Derivatives thereof

Trifluoroacetic Acid (1L) was Charged into a 2L flask under argon and minocycline. HCl (200 g, 1 eq) and N-hydroxymethylphthalimide (100 g) were added to the flask while stirring. Once the entire solid dissolved, H_2SO_4 (200 mL) was added to the reaction. The reaction was heated to 40-50° C. for 5-6 hours. N-hydroxymethylamine (100 g) was added portionwise. When HPLC analysis confirmed that all the starting material was converted to 2,9-bis-aminomethylphthalimidominocycline, the mixture was precipitated out of 4 L of acetone. An exotherm of 15-20° C. was observed. After 1 hour of stirring, the solid was filtered, washed with acetone (200 ml), and dried with the aid of a latex rubber dam. The solid was reslurried in a methanol (1L)/t-BME (2L) mixture and the pH was adjusted to 3 using triethylamine. The solid was filtered and washed with 50 mL of methanol. The yield was 97% of 2,9-bis-aminomethylphthalimideminocycline. 2,9-bis-aminomethylphthalimideminocycline (100 g) was suspended in 2M solution of methylamine in methanol (10 eq). The reaction was stirred at room temperature for 2-3 hours, at which point HPLC analysis confirmed total conversion of the starting material to 2,9-bis aminomethylminocycline. The reaction mixture was poured into t-BME (5 volumes), and stirred for thirty minutes. Next, the suspension

was filtered and washed with t-BME (200 mL) to isolate the desired product, 2,9-bis-aminomethylminocycline. 2,9-bis-aminomethylminocycline (40 g) was slurried in 200 mL water/methanol 1/9 and the pH was adjusted to 3 by the dropwise addition of trifluoroacetic acid. The mixture was heated to 40° C. for 1-2 hours. When HPLC analysis confirmed the hydrolysis of 2,9-bis-aminomethylminocycline to 9-aminomethylminocycline, the reaction was allowed to return to room temperature and the pH was adjusted to 7 using triethylamine. Isopropyl alcohol (200 mL) was added to precipitate out the solid. The product was filtered and washed with 50 mL IPA followed by 100 mL diethyl ether and dried under reduced pressure toisolate 9-aminomethylminocycline.

9-[(Benzylamino)-methyl]-minocycline Dihydrochloride

To 1.0 mmol (600 mg) of 9-(aminomethyl)-minocycline dihydrochloride and in 5 mL of dimethylformamide was added 0.2 mmol (5 mg) of indium trichloride and 1.5 mmol (160 mg) of benzaldehyde at room temperature. After 30 minutes of shaking, 2 mmol (424 mg) of sodium triacetoxyborohydride was added and the reaction was monitored by HPLC. After 1.5 hours, 3 equivalents of triethylamine and 1 equivalent of sodium triacetoxyborohydride. The reaction was complete after 3 hours. The solvent was removed in vacuo and the crude product was purified by preparative HPLC to yield 60 mg of 9-[(benzylamino)-methyl]-minocycline dihydrochloride. LCMS (MH+)=577.

9-[(2,2, dimethyl-propyl amino)-methyl]-minocycline Dihydrochloride

9-(aminomethyl)minocycline (200 mg, 1 eq.), DMF, and trimethylacetaldehyde (45 µl, 1 eq.) were combined in 40 mL flasks and stirred. Triethylamine (150 µL, 3 eq.) was then added. After stirring at room temperature for several minutes, $NaBH(OAc)_3$ (175 mg, 2 eq.) and $InCl_3$ (9 mg, 0.1 eq.) was added. After one hour, the reactions were clear and red. Liquid chromatography showed a single product for the reaction. The reaction was quenched with methanol, the solvent was removed, and the product was purified using column chromatography.

9-[3,4-(Methylenedioxo)phenyl-ureido]-methylminocycline dihydrochloride

To 0.25 mmol (150 mg) of 9-(aminomethyl)-minocycline dihydrochloride and 2 equivalents of triethylamine in 3 mL of dimethylformamide was added 0.5 mmol (81.5 mg) of 3,4-(methylenedioxo)phenyl isocyanate at room temperature. Solution was shaken until reaction was complete (3 hours). Solvent was removed in vacuo and crude product was purified by preparative HPLC to yield 66 mg of 9-[3,4-(methylenedioxo)phenyl-ureido]-methylminocycline dihydrochloride. Yield 41%. LCMS (MH+)=650.

9-[4-(Trifluoromethoxy)phenyl-ureido]-methylminocycline dihydrochloride

To 0.25 mmol (150 mg) of 9-(aminomethyl)-minocycline dihydrochloride and 2 equivalents of triethylamine in 3 mL of dimethylformamide was added 0.5 mmol (101.5 mg) of 4-(trifluoromethoxy)phenyl isocyanate at room temperature. The solution was shaken until the reaction was complete (3 hours). Solvent was removed in vacuo and crude product was purified by preparative HPLC to yield 68 mg of 9-[4-(trifluoromethoxy)phenyl-ureido]-methylminocycline dihydrochloride. Yield 39%. LCMS (MH+)=690.

9-(2'-Phenyl-ethyl-1'-amino)-methyl]-doxycycline

Under an N_2 atmosphere, a stirred solution of 9-aminomethyldoxycycline dihydrochloride (1.21 g, 2.21 mmol) in DMF (10 mL), was treated with $InCl_3$ (0.076 g, 0.34 mmol) and phenylacetaldehyde (0.511 mL; 4.4 mmol). HPLC and LCMS monitoring of the reaction indicated the complete consumption of the starting material over the course of 12 hours. The products were both the mono- (major) and bis-(minor) substituted aminodoxycyclines. Methanol (10 mL) was added to quench the reaction. The reaction mixture was filtered through a bed of Celite, the celite washed with methanol (2x5 mL), and the combined organic layer was concentrated to about 7-8 mL and diluted with ether. The resulting amorphous solid was filtered, washed with ether (6x15 mL) and dried under vacuum to afford a red powder, which was purified by preparative HPLC. The final product was characterized by HPLC, MS, and ^1H NMR spectroscopic methods. MS (m/z): Theor. 577.24; Found: 578.17 (M+1).

EXAMPLE 2

In Vitro Minimum Inhibitory Concentration (MIC) Assay

The following assay is used to determine the efficacy of compounds against common bacteria. 2 mg of each compound is dissolved in 100 µl of DMSO. The solution is then added to cation-adjusted Mueller Hinton broth (CAMHB), which results in a final compound concentration of 200 µg per ml. The compound solutions are diluted to 50 µL volumes, with a test compound concentration of 0.098 µg/ml. Optical density (OD) determinations are made from fresh log-phase broth cultures of the test strains. Dilutions are made to achieve a final cell density of 1×10^6 CFU/ml. At OD=1, cell densities for different genera should be approximately:

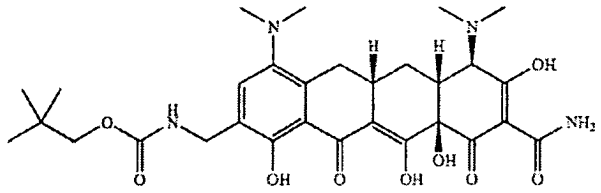
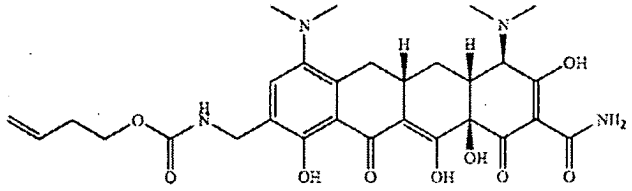
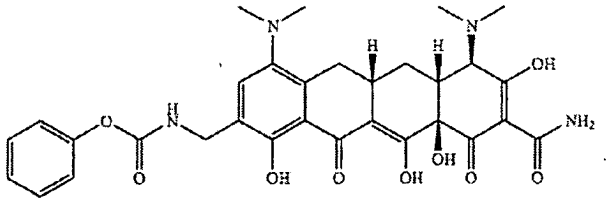
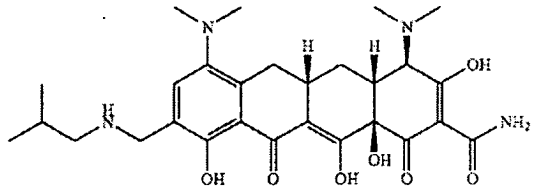
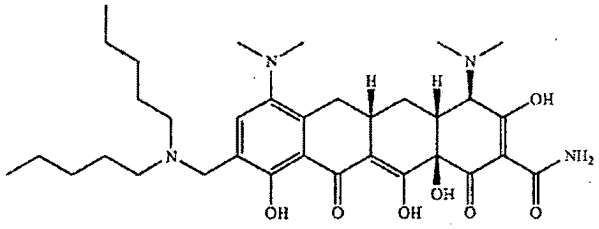
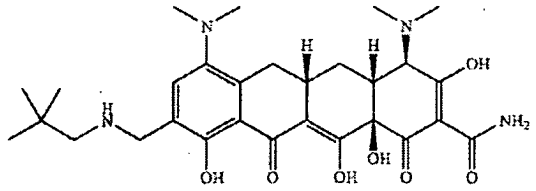
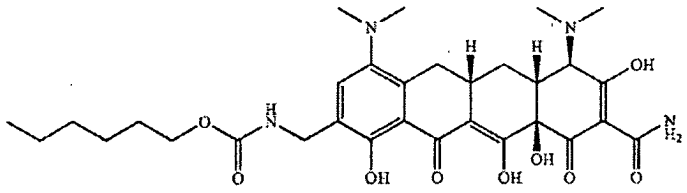
E. coli	1×10^9 CFU/ml
S. aureus	5×10^8 CFU/ml
Enterococcus sp.	2.5×10^9 CFU/ml

50 µl of the cell suspensions are added to each well of microtiter plates. The final cell density should be approximately 5×10^5 CFU/ml. These plates are incubated at 35° C. in an ambient air incubator for approximately 18 hr. The plates are read with a microplate reader and are visually inspected when necessary. The MIC is defined as the lowest concentration of the compound that inhibits growth. Compounds of the invention indicate good inhibition of growth.

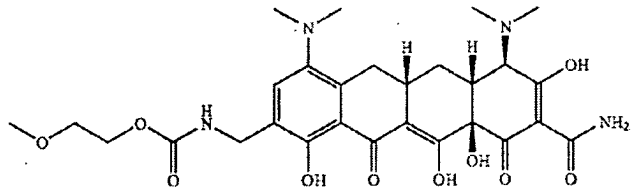
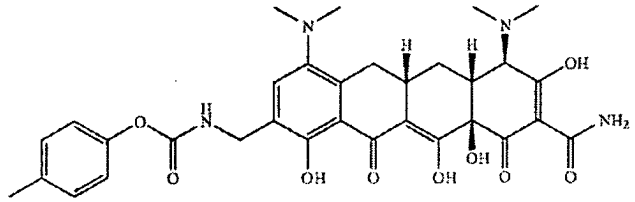
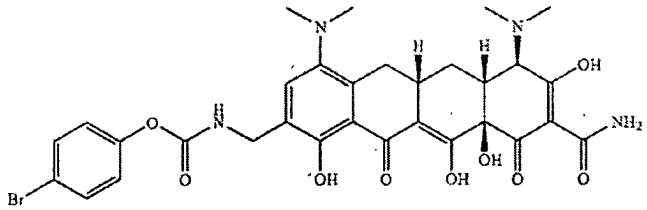
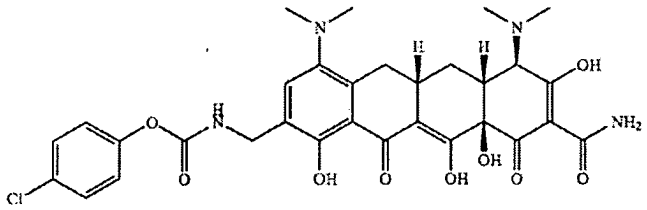
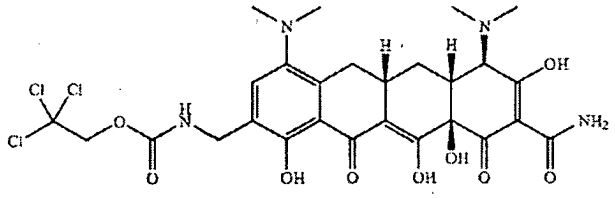
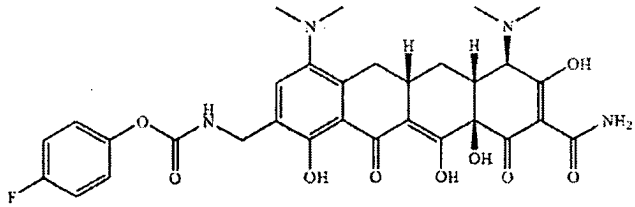
In Table 1, compounds which were good inhibitors of growth of a particular bacteria are indicated with *, compounds which were very good inhibitors of a particular bacteria are indicated with **, and compounds with were particularly good inhibitors of a particular bacteria are indicated with ***.

Equivalents

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures described herein. S Such equivalents are considered to be within the scope of the present invention and are covered by the following claims. The contents of all references, patents, and patent applications cited throughout this application are hereby incorporated by reference. The appropriate components, processes, and methods of those patents, applications and other documents may be selected for the present invention and embodiments thereof.

ID	STRUCTURE	*S. aureus*	*E. hirae*	*E. coli*
NZ		**	**	*
OA		**	**	*
OB		**	**	*
OD		**	NT	***
OG		**	NT	**
OH		***	NT	***
OK		**	NT	**

-continued

ID	STRUCTURE	*S. aureus*	*E. hirae*	*E. coli*
OL		•	NT	•
OM		••	NT	•
ON		••	NT	•
OO		••	NT	••
OP		••	NT	••
OQ		••	NT	•

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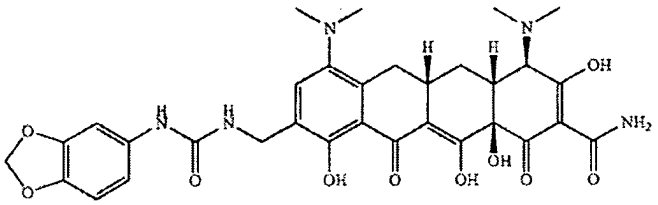
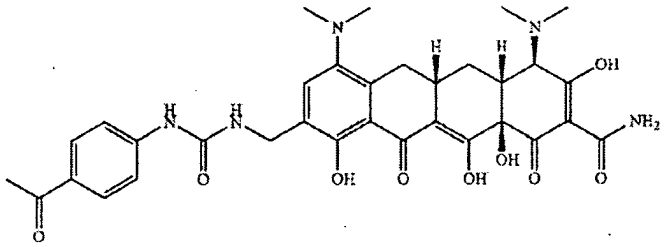
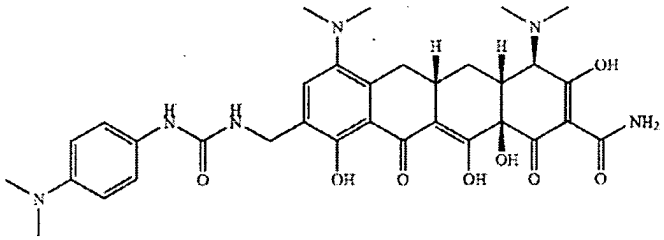
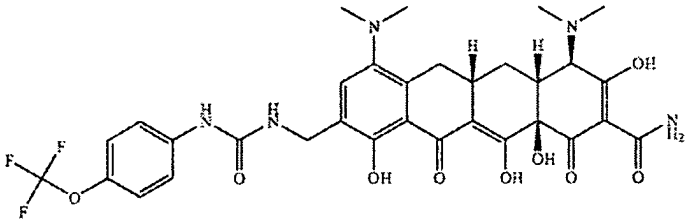
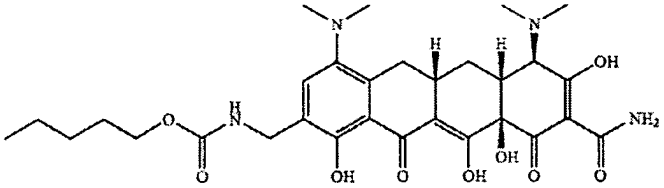
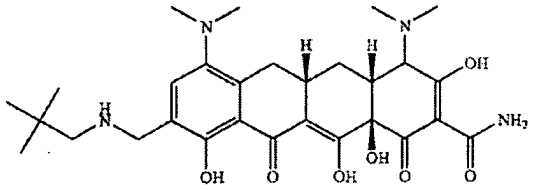
ID	STRUCTURE	*S. aureus*	*E. hirae*	*E. coli*
OR		*	NT	8
OS		*	NT	8
OT		*	NT	*
OU		**	NT	*
OV		**	NT	**
PE		NT	NT	NT

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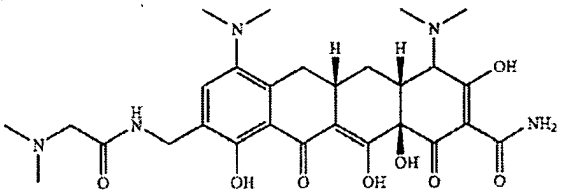
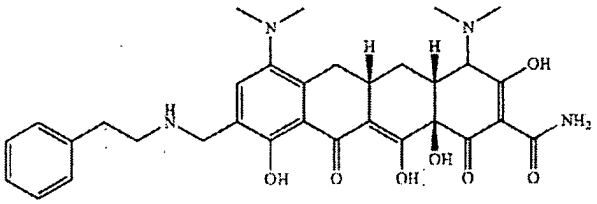
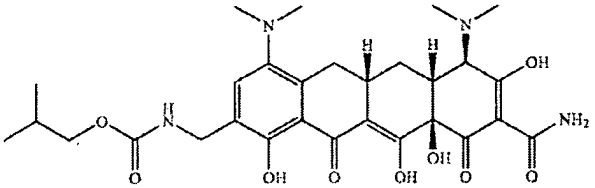
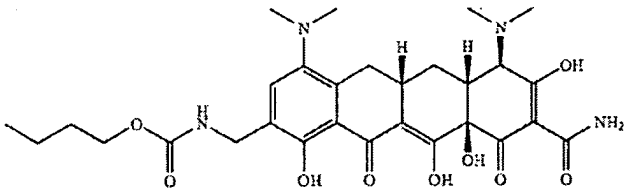
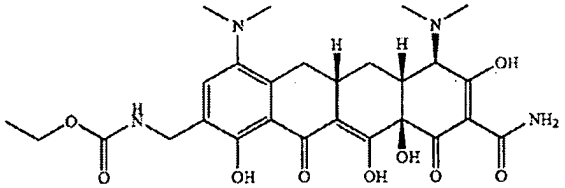
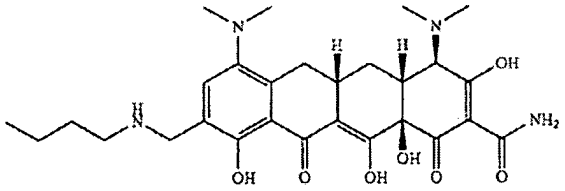
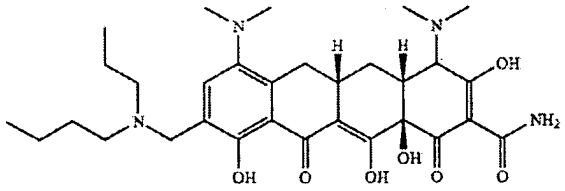
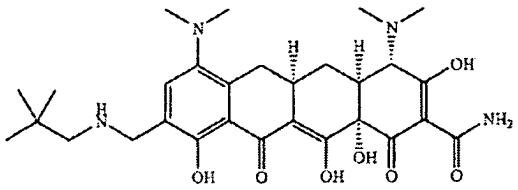
ID	STRUCTURE	*S. aureus*	*E. hirae*	*E. coli*
PM		NT	NT	NT
PQ		NT	NT	NT
PR		NT	NT	NT
PS		NT	NT	NT
PT		NT	NT	NT
PV		NT	NT	NT
PW		NT	NT	NT

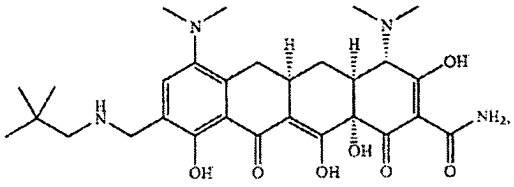
The invention claimed is:

1. A compound of the formula:



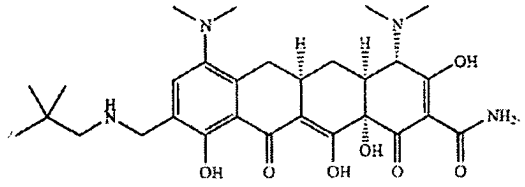
or a pharmaceutically acceptable salt or ester thereof.

2. A compound of the formula:



or a pharmaceutically acceptable salt thereof.

3. A compound of the formula:



4. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any one of claims 1, 2 and 3, and a pharmaceutically acceptable carrier.

* * * * *

EXHIBIT B

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
P.O. BOX 1450
ALEXANDRIA, VA 22313-1450
www.uspto.gov

MCCARTER & ENGLISH, LLP BOSTON
265 Franklin Street
Boston MA 02110

In re Patent No. 7,553,828	:	
Nelson et al.	:	
Issue Date: June 30, 2009	:	
Application No. 10/786,881	:	DECISION ON REQUEST FOR
Filed: February 24, 2004	:	RECONSIDERATION OF
Attorney Dkt. No. 117728-22201	:	PATENT TERM ADJUSTMENT
Title: 9-AMINOMETHYL	:	
SUBSTITUTED MINOCYCLINE	:	
COMPOUNDS	:	

This is a decision on the "APLICATION FOR PATENT TERM ADJUSTMENT INCLUDING REQUEST FOR RECONSIDERATION UNDER 37 C.F.R. § 1.705(d)," filed August 27, 2009, requesting that the patent term adjustment determination for the above-identified patent be changed from three hundred fifty-eight (358) days to seven hundred three (703) days.

The request for reconsideration of patent term adjustment is **DISMISSED**.

On June 30, 2009, the above-identified application matured into US Patent No. 7,553,828 with a patent term adjustment of 358 days. This request for reconsideration of patent term adjustment was timely filed within two months of the issue date of the patent. See 37 C.F.R. § 1.705(d).

The Office acknowledges submission of the $200.00 fee set forth in 37 C.F.R. § 1.18(e). No additional fees are required.

Patentees assert entitlement to a patent term adjustment of 703 days. Patentees maintain the 345 of 856 days delay under § 154(b)(1)(B) do not overlap with the delay under § 154(b)(1)(A). Thus, patentees request that the determination of patent term adjustment be increased to a total of seven hundred three (703) days (the sum of the period of three-year delay (856 days) and

the period of examination delay (570 days) minus applicants' delay (212 days) minus time consumed by the request for continued examination (RCE) pursuant to 37 CFR 1.703(b)(1) (491 days) minus time consumed by filing of the Notice of Appeal pursuant to 37 CFR 1.703(b)(4) (20 days))[1]. Patentees do not dispute the 212-day reduction for applicants' delay.

The Office finds that as of the day before the filing of the request for continued examination (RCE) on February 25, 2008, the application was pending three years and 366 days after its filing date (February 25, 2007 to February 25, 2008). At the time of filing of the RCE on February 26, 2008, a period of adjustment of 535 days was entered for Office delay pursuant to 37 CFR 1.702(a)(1). At issue is whether patentee should accrue an additional 366 days of patent term adjustment for the Office taking in excess of three years to issue the patent as well as 535 days for Office failure to take a certain action within a specified time frame (or examination delay).

The Office contends that the entire 366-day period of delay in issuance of the patent overlaps with the period of 535 days of examination delay. Patentees' calculation of the period of overlap is inconsistent with the Office's interpretation of this provision. 35 U.S.C. 154(b)(2)(A) limits the adjustment of patent term, as follows:

> To the extent that the periods of delay attributable to grounds specified in paragraph (1) overlap, the period of any adjustment granted under this subsection shall not exceed the actual number of days the issuance of the patent was delayed.

Likewise, 37 CFR 1.703(f) provides that:

> To the extent that periods of delay attributable to the grounds specified in §1.702 overlap, the period of adjustment granted under this section shall not exceed the actual number of days the issuance of the patent was delayed.

As explained in *Explanation of 37 CFR 1.703(f) and of the United States Patent and Trademark Office Interpretation of 35 U.S.C.*

[1] As 37 CFR 1.702(b)(4) is not applicable to the instant prosecution history, consideration of a 20 day overlap under 37 CFR 1.703(b)(4) as discussed by patentees is not warranted.

154(b)(2)(A), 69 Fed. Reg. 34283 (June 21, 2004), the Office interprets 35 U.S.C. 154(b)(2)(A) as permitting either patent term adjustment under 35 U.S.C. 154(b)(1)(A)(i)-(iv), or patent term adjustment under 35 U.S.C. 154(b)(1)(B), but not as permitting patent term adjustment under both 35 U.S.C. 154(b)(1)(A)(i)-(iv) and 154(b)(1)(B). Accordingly, the Office implements the overlap provision as follows:

> If an application is entitled to an adjustment under 35 U.S.C. 154(b)(1)(B), the entire period during which the application was pending (except for periods excluded under 35 U.S.C. 154(b)(1)(B)(i)-(iii)), and not just the period beginning three years after the actual filing date of the application, is the period of delay under 35 U.S.C. 154(b)(1)(B) in determining whether periods of delay overlap under 35 U.S.C. 154(b)(2)(A). Thus, any days of delay for Office issuance of the patent more than 3 years after the filing date of the application, which overlap with the days of patent term adjustment accorded prior to the issuance of the patent will not result in any additional patent term adjustment. See 35 U.S.C. 154(b)(1)(B), 35 U.S.C. 154(b)(2)(A), and 37 CFR § 1.703(f). See *Changes to Implement Patent Term Adjustment Under Twenty Year Term; Final Rule*, 65 Fed. Reg. 56366 (Sept. 18, 2000). See also *Revision of Patent Term Extension and Patent Term Adjustment Provisions; Final Rule*, 69 Fed. Reg. 21704 (April 22, 2004), 1282 Off. Gaz. Pat. Office 100 (May 18, 2004). See also *Explanation of 37 CFR 1.703(f) and of the United States Patent and Trademark Office Interpretation of 35 U.S.C. 154(b)(2)(A)*, 69 Fed. Reg. 34283 (June 21, 2004).

As such, the period for over 3 year pendency does not overlap only to the extent that the actual dates in the period beginning three years after the date on which the application was filed overlap with the actual dates in the periods for failure of the Office to take action within specified time frames.

In this instance, the relevant period under 35 U.S.C. 154(b)(1)(B) in determining whether periods of delay "overlap" under 35 U.S.C. 154(b)(2)(A) is the entire period during which the application was pending before the Office, February 24, 2004 until the day before the filing of the RCE on February 25, 2008. 535 days of patent term adjustment were accorded prior to the filing of the RCE for the Office failing to respond within

specified time frames during the pendency of the application. All of the 366 days for Office delay in issuing the patent overlap with the 535 days of Office delay accrued prior to submission of the RCE. Entry of both 366 days pursuant to 37 CFR §1.702(b) for the Office taking in excess of three years to issue the patent and 535 days pursuant to 37 CFR §1.702(a)(1) for Office examination delay is neither permitted nor warranted. The Office did not delay 535 days and then another 366 days. As of the filing of the RCE on February 26, 2008, the greater period, 535 days, is the actual number of days issuance of the patent was delayed by the Office. An additional 35-day patent term adjustment was accorded subsequent to the filing of the RCE.

Accordingly, at issuance, the Office properly entered no additional days of patent term adjustment for the Office taking in excess of 3 years to issue the patent, having considered the 535 days of examination delay under 37 CFR 1.702(a)(1) that occurred prior to the filing of the RCE as well as the 35 days of examination delay under 37 CFR 1.702(a)(2) that occurred subsequent to the filing of the RCE, as well as the applicant delays of 212 days under 37 CFR 1.704.

In view thereof, no adjustment to the patent term will be made.

Telephone inquiries specific to this matter should be directed to Charlema Grant, Petitions Attorney, at (571) 272-3215.

/ALESIA M. BROWN/

Alesia M. Brown
Petition Attorney
Office of Petitions